Comparative Effectiveness Review
Number 260

Nutrition as Prevention for Improved Cancer Health Outcomes

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

A representative from AHRQ served as a Contracting Officer's Representative and reviewed the contract deliverables for adherence to contract requirements and quality. AHRQ did not directly participate in the literature search, determination of study eligibility criteria, data analysis, interpretation of data, or preparation or drafting of this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The National Institutes of Health Office of Disease Prevention requested this report from the EPC Program at AHRQ to inform a Pathways to Prevention Workshop. The NIH Office of Disease Prevention provided the funding for this report through an Inter-Agency Agreement with AHRQ. AHRQ assigned this report to the following EPC: Minnesota Evidence-based Practice Center (Contract Number: 75Q80120D00008).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

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Nutrition as Prevention for Improved Cancer Health Outcomes

Structured Abstract

Objective. To understand the evidence base for nutrition interventions delivered prior to or during cancer treatment for preventing and treating negative cancer and cancer treatment–related outcomes among individuals with or at risk for malnutrition. The primary purpose was to inform the National Institutes of Health (NIH) Pathways to Prevention workshop *Nutrition as Prevention for Improved Cancer Health Outcomes*, held July 26–28, 2022.

Data sources. We searched Ovid Medline®, Ovid Embase®, and Cochrane Central Register of Controlled Trials to identify studies from 2000 through July 2022. We conducted grey literature searches to identify additional resources relevant to the associated costs or value (e.g., cost-effectiveness, cost-benefit) of nutrition interventions.

Review methods. The review was guided by a set of Key Questions established by the NIH planning committee for the *Nutrition as Prevention for Improved Cancer Health Outcomes* workshop. We searched for studies that evaluated a broad range of nutrition interventions (e.g., dietary supplements, nutrition support, nutrition counseling) for preventing and treating negative outcomes of cancer and cancer-related treatment. Eligible studies included randomized controlled trials (RCTs) with enrollment ≥50 participants. We extracted basic study information from all eligible studies, then grouped studies by broad intervention and cancer types. We provide a detailed evidence map for all included studies, but conducted risk of bias and additional qualitative descriptions of outcomes for only those intervention and cancer types with a larger volume of literature.

Results. We identified 9,798 unique references, with 206 studies from 219 publications reporting RCTs of nutrition interventions to potentially improve negative outcomes of cancer and cancer-related treatment. Two decades of randomized trial evidence on nutrition interventions for adults prior to and/or during cancer treatment primarily focused on dietary supplements, nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions for gastrointestinal and head and neck cancers in the inpatient setting. Most studies evaluated changes in body weight/composition, adverse events, length of hospital stay, and quality of life. Few studies were conducted within the U.S. setting. Among intervention and cancer types with a high volume of literature (n=114), which predominantly included studies in dietary supplements and nutrition support in gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias, and 49 percent (n=56) high risk of bias (lower quality). Low and medium risk-of-bias studies reported mixed results on the effect of nutrition interventions across cancer and treatment-related outcomes. Although the evidence map shows a large volume of studies evaluating nutrition interventions and outcomes, these studies showed high heterogeneity across study populations, interventions, and outcomes (measure definitions, timing of measurements), even within nutrition intervention categories; as a result, we could not aggregate results. While studies enrolled individuals from multiple cancer types, treatments, and stages, across the lifespan, with varying degrees of muscle

wasting, and in those with a range of comorbid conditions, no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Among studies included in our Key Questions, we found that few (4%, n=8) published cost or value (e.g., cost-effectiveness, cost-benefit) information related to the intervention. In our grey literature search of additional studies examining cost or value of nutrition interventions, we found few studies that conducted cost-effectiveness or cost-benefit analyses; among those that did, we found the studies were conducted in non-U.S. health systems and demonstrated mixed results on the value of nutrition interventions.

Conclusions. Although overall RCT evidence focused on a wide range of nutrition interventions, studies were concentrated in use of dietary supplements, nutrition support, and the route or timing of nutrition interventions within gastrointestinal and head and neck cancers in inpatient settings. Among interventions with the highest volume of literature, the majority of studies were rated as high risk of bias. Our findings point to the need for rigorous new research to bolster the evidence base. Specifically, the field needs a more detailed future evaluation of a subset of nutrition interventions contained in this evidence map that focuses on priorities most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers). Further, studies should be specifically designed to evaluate the main outcomes of interest for clinical practice. Future research would also benefit from creation of standardized taxonomies for interventions and outcomes as well as more rigorous design and reporting of nutrition interventions. As mentioned, heterogeneity of populations, interventions, comparators, and outcomes precluded aggregation. Currently, the quality and heterogeneity of the studies limit translation of findings into clinical practice or guidelines. In order to inform development of these guidelines, coordinated efforts are required to develop detailed conceptual frameworks for mechanisms of nutrition interventions most relevant to clinical care providers and patients. Such frameworks would help inform priorities for future research as well as guide practice and policy.

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Executive Summary

Main Points

- Two decades of randomized trial evidence from 206 studies of nutrition interventions in adults prior to and/or during cancer treatment focused on use of dietary supplements (not including vitamins and minerals), nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions. Studies were predominately conducted in individuals with gastrointestinal and head and neck cancers, with few studies conducted within the U.S. setting.
- Studies focused on evaluating changes in body weight/composition, adverse events, length of hospital stay, and quality of life.
- Among studies with a high volume of literature (n=114), which predominately examined dietary supplements and nutrition support in gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias and 49 percent (n=56) as high risk of bias (lower quality).
- Low- and medium-risk-of-bias studies reported mixed results on the effect of nutrition interventions across outcomes for cancer and cancer treatment (detailed in the evidence summary results below).
- Among studies included in our Key Questions, few (4%, n=8) studies reported a formal evaluation of the value of the nutrition interventions (e.g., cost-effectiveness, cost-benefit) or provided costs detailed by intervention component; generally, these studies reported only overall costs from inpatient non-U.S. settings. In our grey literature search, we found few studies that conducted cost-effectiveness or cost-benefit analyses, and, among those, we found mixed results on the value of nutrition interventions in non-U.S. health systems.
- Future research would benefit from studies focused on priorities and interventions most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers). Future studies could then be specifically designed to evaluate the main outcomes of interest relevant for clinical practice.
- Future research would also benefit from a creation of standardized taxonomies for interventions and outcomes as well as more rigorous design and reporting of nutrition interventions.

Background and Purpose

Among adults with cancer, malnutrition is associated with decreased treatment completion, more use of healthcare, and worse survival.[1-4] Prevalence of malnutrition is high among adults with cancer,[5-7] but only 30 to 50 percent of cancer patients at risk for malnutrition receive nutrition support or intervention.[8, 9] No high-quality guidelines exist with recommendations for preventing or treating malnutrition in adults with cancer, potentially due to several factors, including: (1) the broad range of criteria that define malnutrition, (2) variability of nutrition interventions (from medical nutrition therapy to optimize body weight or muscle mass to dietary supplements intended to replace specific micronutrient deficiencies), and (3) the lack of cohesive evidence-based approaches to malnutrition in this population.

This systematic review sought to examine the current evidence for the effectiveness of providing nutrition interventions before or during cancer therapy to improve outcomes for cancer

and cancer treatment, with the goal of informing stakeholders about relevant research gaps and challenges. Findings from the review informed discussions among experts and stakeholders at the National Institutes of Health (NIH) Pathways to Prevention (P2P) workshop, *Nutrition as Prevention for Improved Cancer Health Outcomes*, which took place July 26-28, 2022. In addition, our review aims to contribute to the development of a research agenda for evaluating nutrition interventions in inpatient and outpatient cancer care. Results may help inform clinical guidelines on prevention and treatment of malnutrition in cancer care by providing a summary and synthesis of the available evidence for clinical and policy stakeholders to use in the development of such guidelines.

Methods

The methods for this systematic review follow the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews and the PRISMA reporting guidelines.[10] See the review protocol (https://effectivehealthcare.ahrq.gov/products/improved-cancer -outcomes/protocol) and the methods appendix for additional details. The review was guided by a set of Key Questions, which were established by the NIH planning committee for the *Nutrition as Prevention for Improved Cancer Health Outcomes* workshop. Briefly, we searched Ovid Medline®, Ovid Embase®, and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials published and indexed in bibliographic databases from 2000 through July 2022. We also conducted grey literature searches to identify additional resources relevant to cost-effectiveness.

Results

We identified 9798 unique references, with 206 studies from 219 publications reporting findings from randomized controlled trials (RCTs) of nutrition interventions to improve negative outcomes from cancer treatment. Overall, we found two decades of randomized trial evidence on nutrition interventions for adults prior to and/or during cancer treatment. This evidence focused on use of dietary supplements, nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions. Studies were predominately conducted in populations with gastrointestinal and head and neck cancers, and included both inpatient surgical and outpatient settings. Most of the studies were conducted outside of the United States. Studies focused on evaluating changes in body weight/composition, adverse events, length of hospital stay, and quality of life. Few studies were conducted within the U.S. setting. Among studies with a high volume of literature, which predominately included studies in dietary supplements and nutrition support in gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias and 49 percent (n=56) high risk of bias (lower quality).

Low- and medium-risk-of-bias studies, reported mixed results on the effect of nutrition interventions outcomes for cancer and cancer treatment. Among eight low- or medium-risk-of-bias studies in nutrition support prior to cancer treatment, studies reported mixed results on development of complications, improvements in weight loss, and length of hospital stay.[11-18]

Among studies initiated prior to and continuing through cancer treatment, four medium-risk-of-bias studies across five publications showed mixed results for the effect of dietary supplements on weight changes, readmissions, length of hospital stay, development of complications, and survival.[19-23] Two low- and four medium-risk-of-bias study of nutrition

support reported mixed results, with some studies reporting a benefit and some reporting no difference in reducing adverse events, readmissions, length of hospital stay, and survival.[24-30]

Among four low- and 14 medium-risk-of-bias studies of dietary supplements conducted during cancer treatment, results were mixed, with most studies reporting no benefit of added dietary supplements on body weight, adverse events, length of hospital stay, or survival.[31-45] Two low-risk-of-bias studies reported fewer adverse events and decreased length of hospital stay with soybean and fish oil.[34, 45] One medium-risk-of-bias study of glutamine reported improved body weight, reduction in adverse events, and improved treatment tolerance,[38] while another medium-risk-of-bias study reported fewer adverse events among those using branch chain amino acid (BCAA)-enriched total parenteral nutrition (TPN).[40] Another medium-risk-of-bias study found improvement in postoperative complications with enteral and parenteral nutrition supplemented with omega-3 fatty acids.[44] Three studies reported improvements in length of hospital stay across diverse supplements.[32, 43, 46]

One low- and 10 medium-risk-of-bias studies that examined route and timing of nutrition interventions conducted during cancer treatment demonstrated mixed results.[47-57] The majority reported no difference for body weight, adverse events, readmissions, or death, but half reported reduced length of hospital stay. One low-risk-of-bias study reported that postoperative enteral nutrition reduced adverse events length of hospital stay.[48] Among three low- and eight medium-risk-of-bias studies that examined nutrition support (including oral nutrition) during cancer treatment,[58-72] results were mixed for body weight, nutrition status, and adverse events. Two low-[66, 71] and three medium-risk-of-bias studies[67, 69, 72] reported improvements in body weight or composition with postoperative nutrition support. Four out of ten studies[58, 59, 65, 70] reported improvements in adverse events and three reported improvements in length of hospital stay[58, 59, 70] across diverse enteral and oral nutrition support interventions.

Finally, among studies of the effects of nutrition interventions on symptoms, three medium-risk-of-bias studies in dietary supplements reported mixed results for patient-reported symptoms.[33 23, 43] One study of probiotics and omega-3 fatty acids reported improved quality of life,[33] while another reported no benefit.[23] Two studies reported mixed outcomes for patient-reported symptoms with one reporting a benefit[33] and one no difference.[43] Among five low- and four medium-risk-of-bias study of nutrition support, reported results were mixed.[13, 15, 16, 18, 28, 66, 68, 69, 71, 72] Two studies showed mixed results on functional status, with one showing a benefit and one no difference.[28, 66] Two low-risk-of-bias studies reported improvement in nausea for individuals receiving preoperative oral carbohydrate drinks.[28, 66] A third low-risk-of-bias study reported improvement in treatment tolerance and symptoms after use of oral nutrition supplements and dietary advice.[66, 68]

While studies addressing Key Questions (KQs) 1-3 enrolled individuals from multiple cancer types, treatments, and stages (KQ 1-3a) across the lifespan (KQ 1-3b), with varying degrees of muscle wasting (KQ 1-3c), and in those with a range of comorbid conditions (KQ 1-3d), no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Only four studies reported the effects of nutrition interventions intended for weight loss using special diets among individuals with breast cancer and assessed body weight and composition changes. One study reported on each of the following symptoms: quality of life, symptoms, and treatment tolerance.

Among studies included in our KQ we found that few (4 percent, n=8) published cost or value (e.g., cost-effectiveness, cost-benefit) information related to the intervention. In our grey

literature search of additional studies examining cost or value of nutrition interventions, we found few studies that conducted cost-effectiveness or cost-benefit analyses, and, among those, found mixed results on the value of nutrition interventions; most of these studies were conducted in non-U.S. health systems.

Limitations

The methods we used for this systematic review provided a detailed evidence map of the current state of literature on nutrition interventions, highlighting not only concentrations of literature but also gaps in intervention types. We purposefully chose broad definitions of nutrition interventions, thereby increasing the scope, breadth, and heterogeneity of the included literature in order to better assess the range and depth of available evidence. This decision allowed for demonstration of the diffuse literature set on the topic and highlighted the predominantly low quality of studies where there were concentrations of similar intervention types. However, this required focusing on high-level directionality of intervention effects across a broader range of nutrition interventions rather than looking for more detailed, precise estimates of intervention effects. Overall, this approach allowed for high level mapping of the evidence across Key Questions by patient, intervention, comparator, and outcome categories. It also revealed evidence gaps for future research.

Implications and Conclusions

Overall, the RCT evidence focused on a wide range of nutrition interventions, but studies were concentrated in use of dietary supplements (not including vitamins and minerals), nutrition support, and the route or timing of nutrition interventions within gastrointestinal and head and neck cancers in the inpatient setting of hospitals outside of the United States. Among interventions with the highest volume of literature, a majority of studies were evaluated as having high risk of bias. Our findings point to the need for rigorous new U.S.-based research to bolster the evidence base. Specifically, the field needs a more detailed future evaluation of a subset of nutrition interventions contained in this evidence map that focus on priorities most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers). Further, studies should be specifically designed to evaluate the main outcomes of interest for clinical practice. Future research would also benefit from creation of standardized taxonomies for interventions and outcomes as well as more rigorous design and reporting of nutrition interventions. As mentioned, heterogeneity of populations, interventions, comparators and outcomes precluded aggregation. Currently, the quality and heterogeneity of the studies limit the ability to translate findings into clinical practice or guidelines. In order to inform development of guidelines, coordinated efforts are required to establish detailed conceptual frameworks for mechanisms of nutrition interventions most relevant to clinical care providers and patients. Such frameworks would help inform priorities for future research as well as guide practice and policy.

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Chapter 1. Introduction

Background and Objective for Systematic Review

Among adults with cancer, malnutrition is associated with decreased treatment completion, greater healthcare use, and worse survival.[1-4] Cancer-related malnutrition[5] results from inadequate nutrition intake due to the systemic effects of the disease, psychological effects or adverse effects of treatment, and other factors.[6] Malnutrition can result in micronutrient deficiencies, deplete body fat and/or lean mass, create alterations in metabolism, and lead to reduced physical function and poor health outcomes (both cancer-related and other).[7] Adults with cancer commonly experience malnutrition, with estimates ranging between 25 to 80 percent across patient populations.[8-10] However, malnutrition varies substantially by patient characteristics such as age at diagnosis, tumor type, stage of disease, type of cancer treatment, and pre-existing conditions (e.g., diabetes), among other factors.[9, 11] Further, many factors may increase risk or severity of malnutrition including cancer symptoms (e.g., anorexia, early satiety, and fatigue), treatment complications (e.g., mucositis, nausea, taste changes), and psychological distress.[12] In individuals with cancer, malnutrition often goes unrecognized —not only by providers during clinical assessment, but also by patients and caregivers.[13] Even when it is recognized, malnutrition may not be adequately addressed. Only 30 to 50 percent of cancer patients at risk for malnutrition receive nutrition intervention.[14, 15] Considering that an estimated 1.9 million individuals were diagnosed with cancer in 2021, between 570,000 and 950,000 individuals may be at risk for malnutrition.[16]

Both the American Society for Parenteral and Enteral Nutrition and the European Society for Clinical Nutrition and Metabolism recommend initial malnutrition screening and subsequent periodic reassessment during the course of cancer treatment and survivorship.[7, 12] However, no guidelines based on comprehensive, high-quality evidence exist to screen or treat malnutrition in adults with cancer. Guideline development may be challenged by the broad range of criteria defining malnutrition, variability of nutrition interventions (from medical nutrition therapy to optimize body weight or muscle mass to dietary supplements intended to replace specific micronutrient deficiencies) and by the lack of cohesive evidence-based approaches to identify and address malnutrition in this population. This leaves cancer patients and their providers with decisional dilemmas. Furthermore, we do not know how treatment benefits and harms may be affected by patient characteristics (e.g., age, race/ethnicity, family/other support, social economic status including food security, pre-diagnosis obesity or underweight), cancer-related factors (e.g., cancer type, stage), treatment type (chemotherapy, radiation, surgery), treatment timing (before or after treatment) and provider/hospital/geographic characteristics (e.g., presence of integrated nutrition programs; specialist type, availability, and insurance coverage; and rural/urban location). Considering the poor access to outpatient nutrition care for cancer patients across the United States,[17] understanding the most effective interventions for nutrition in this population is critical.

Medical nutrition therapy seeks to address current cancer issues and minimize side effects related to cancer treatment. Nutrition therapy may encompass a broad range of interventions such as nutrition and behavioral counseling, nutrition support (including oral nutrition supplements) or use of dietary supplements that vary in terms of timing and resources required to implement. Because nutrition therapies vary widely, and because settings differ greatly in their capacity to administer and support these interventions (particularly in outpatient settings), we need to better

understand their effectiveness at improving outcomes of cancer and cancer treatment among adults at risk for cancer-associated malnutrition. More clarity around which interventions or components of interventions work best and in which settings and situations will help patients, caregivers, and providers make more informed decisions and guide future research to close evidence gaps.

Purpose and Scope

The purpose of this systematic review is to examine the current evidence for how nutrition interventions before or during cancer therapy affect outcomes of cancer and cancer treatment, with a focus on research gaps and opportunities. Findings from this review informed discussion of experts and stakeholders at the National Institutes of Health Pathways to Prevention (P2P) workshop, *Nutrition as Prevention for Improved Cancer Health Outcomes,* held July 26-28, 2022 (https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/nutrition-prevention-improved-cancer-health-outcomes). Because our results describe the current body of scientific evidence, they may also be useful for shaping clinical guidelines on prevention and treatment of malnutrition in cancer care, and provide a summary and synthesis of the available evidence for clinical and policy stakeholders to apply in the development of such guidelines.

Report Organization

Chapter 2 outlines the methods used to conduct this systematic review. Chapter 3 presents the overall results of the search for the review's eligible studies. Chapter 4 summarizes the evidence map across Key Questions (KQs). Chapter 5 presents results from KQ1 that examined nutrition interventions that were only delivered prior to the initiation of cancer treatment. Chapter 6 separately presents studies of interventions that were initiated prior to and continued after cancer treatment (KQs 1 and 2). Chapter 7 presents results from KQ2 that were delivered only after treatment began. Chapters 8 and 9 address KQ3, and KQ4, respectively. Chapter 10 presents results for the Contextual Question. Chapter 11 discusses research gaps and future research considerations. An overview of key terms for the report is provided in Table 1.1. A complete list of acronyms can be found at the end of this report.

Table 1.1 Key terms

Term	Description
Eligible study	An **eligible study** is one that meets the initial study criteria that were defined in advance regarding the type of study that would be included in the systematic or comparative effectiveness review.
Evidence Map	A systematic search of a broad field to identify gaps in knowledge and/or future research needs.[18]
Nutrition Interventions	Given that there is no agreed-upon classification system for grouping or describing non-pharmacologic nutrition interventions, we classified interventions based on the content and intent of the intervention and the intended audience, using taxonomies and definitions where available. Nutrition intervention categories include: nutrition counseling, dietary supplements (not including vitamins and minerals), special diets, route or timing of nutrition interventions, nutrition support (including oral nutrition supplements), and multi-component interventions. Detailed descriptions of studies falling within each category can be found in Chapter 2.
Pre-treatment nutrition interventions	**Pre-treatment nutrition interventions** includes any intervention delivered from the date of diagnosis through the initiation of cancer-directed therapy.

Term	Description
Nutrition Interventions during cancer therapy	**Nutrition interventions during cancer therapy** include interventions delivered simultaneously (at least in part) with cancer therapy (e.g., systemic therapy, radiation, surgery, endocrine therapy), regardless of treatment intent (e.g., curative vs. palliative).
Cancer Type	Studies were classified by cancer type of the enrolled participants. Cancer type was based on site at diagnosis and grouped into broad categories based on related organ systems and where the literature was concentrated. Categories included gastrointestinal (e.g., stomach, colon, rectal), head and neck (e.g., laryngeal), and multiple cancers (i.e., enrolled patients with multiple distinct cancer types such as breast, lung and prostate cancer combined). The remaining studies enrolled individuals from a broad range of single cancer types (e.g., lymphoma) that did not represent a large volume of literature and were grouped into an 'Other Cancer Type' for analysis.
Risk of bias	**Risk of bias** is the extent to which the design and conduct of a study are likely to have prevented bias in the results.
At-risk for malnutrition	Given there are a wide variety of approaches to determining an individual's risk for cancer-associated malnutrition, ranging from use of validated screening tools to considering any individual with cancer as at-risk, we used author definitions of 'at-risk for malnutrition' in our reporting. However, we do indicate when specific tools or criteria were used to evaluate malnutrition within the results.

Chapter 2. Methods

Review Approach

The methods for this systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). This systematic review also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).[19] The final protocol was posted online on October 8, 2021 (https://effectivehealthcare.ahrq.gov/products/improved-cancer-outcomes/protocol). We registered the protocol on PROSPERO (CRD42021282881).

Research (Key) Questions

This review addressed four Key Questions (KQs) to evaluate the effects of nutrition interventions on outcomes of cancer and cancer treatment. Nutrition interventions can be very heterogeneous which may affect the cost and resources needed to deliver the interventions. Therefore, the review also included a Contextual Question to provide information on the cost-effectiveness of nutrition interventions.

Key Questions for Systematic Review

- KQ1: In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutrition interventions prior to cancer treatment in preventing negative treatment outcomes such as effects on dose tolerance, hospital utilizations, adverse events, and survival?
  - **KQ1a:** Do the effects of nutrition interventions on preventing the negative outcomes associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery), and stage of disease?
  - **KQ1b:** Do the effects of nutrition interventions vary across the lifespan (e.g., adults aged ≥65 years vs. <65 years)?
  - **KQ1c:** Compared to adults without muscle wasting, do nutrition interventions prevent the negative outcomes associated with cancer treatment in adults with muscle wasting?
  - **KQ1d:** Do the effects of nutrition interventions on preventing the negative outcomes associated with cancer treatment vary across special populations (e.g., individuals with multiple comorbid conditions)?
- **KQ2:** In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutrition interventions ***during*** cancer treatment in preventing negative treatment outcomes such as effects on dose tolerance, hospital utilizations, adverse events, and survival?
  - **KQ2a:** Do the effects of nutrition interventions on preventing the negative outcomes associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery), and stage of disease?

- **KQ2b:** Do the effects of nutrition interventions vary across the lifespan (e.g., adults aged ≥65 years vs. <65 years)?
- **KQ2c:** Compared to adults without muscle wasting, do nutrition interventions prevent the negative outcomes associated with cancer treatment in adults with muscle wasting?
- **KQ2d:** Do the effects of nutrition interventions on preventing the negative outcomes associated with cancer treatment vary across special populations (e.g., individuals with multiple comorbid conditions)?

- **KQ3:** In adults diagnosed with cancer who have or are at risk for cancer-associated malnutrition, what is the effect of nutrition interventions ***prior to*** or ***during*** cancer treatment on associated symptoms such as fatigue, nausea and vomiting, appetite, physical and functional status (e.g., frailty), and quality of life?
  - **KQ3a**: Do the effects of nutrition interventions on symptoms associated with cancer treatment vary by cancer type, treatment type (chemotherapy, radiation, surgery), and stage of disease?
  - **KQ3b:** Do the effects of nutrition interventions vary across the lifespan (e.g., adults aged ≥65 years vs. <65 years)?
  - **KQ3c:** Compared to adults without muscle wasting, do nutrition interventions differentially affect symptoms associated with cancer treatment in adults with muscle wasting?
  - **KQ3d:** Do the effects of nutrition interventions on symptoms associated with cancer treatment vary across special populations (e.g., individuals with multiple comorbid conditions)?
- **KQ4:** In adults with cancer who are overweight or obese, what is the effect of nutrition interventions intended for weight loss ***prior to*** or ***during*** cancer treatment in preventing negative treatment outcomes such as effects on dose, hospital utilizations, adverse events, and survival?

Contextual Question

1. What evidence is available on the cost-effectiveness of nutrition interventions for preventing negative outcomes associated with cancer treatment?

Table 2.1 provides details on the population, interventions, comparators, outcomes, timing, and setting for the research questions.

Table 2.1. Population, intervention, comparator, outcome, timing, and setting (PICOTS)

Element	KQ1: Pre-Treatment Nutrition Interventions)	KQ2: Nutrition Interventions During Treatment	KQ3: Pre- or During Treatment Nutrition Interventions and Patient-Centered Outcomes	KQ4: Weight Loss in Overweight/Obese Adults With Cancer
Population	Adults diagnosed with cancer at or after age 18 who have or are at risk for cancer-associated malnutrition Subgroups: • Cancer and treatment characteristics (cancer type, treatment type (systemic therapy, radiation, surgery), stage of disease) • Adults ≥65y vs younger • Muscle wasting (e.g., sarcopenia, cachexia, pre-cachexia) vs. no muscle wasting Special populations (individuals with multiple comorbid conditions)	Adults diagnosed with cancer at or after age 18 who have or are at risk for cancer-associated malnutrition Subgroups: • Cancer and treatment characteristics (cancer type, treatment type (systemic therapy, radiation, surgery), stage of disease) • Adults ≥65y vs younger • Muscle wasting (e.g., sarcopenia, cachexia, pre-cachexia) vs. no muscle wasting Special populations (individuals with multiple comorbid conditions)	Adults diagnosed with cancer at or after age 18 who have or are at risk for cancer-associated malnutrition Subgroups: • Cancer and treatment characteristics (cancer type, treatment type (systemic therapy, radiation, surgery), stage of disease) • Adults ≥65y vs younger • Muscle wasting (e.g., sarcopenia, cachexia, pre-cachexia) vs. no muscle wasting Special populations (individuals with multiple comorbid conditions)	Overweight (BMI 25-<30)/obese (BMI ≥30) adults ≥18y of age diagnosed with cancer

Element	KQ1: Pre-Treatment Nutrition Interventions)	KQ2: Nutrition Interventions During Treatment	KQ3: Pre- or During Treatment Nutrition Interventions and Patient-Centered Outcomes	KQ4: Weight Loss in Overweight/Obese Adults With Cancer
Intervention	Nutrition interventions under the supervision of a nutrition professional (e.g., dietitian, nutritionist, or other licensed clinicians) • Diet or nutrition therapy (via oral or enteral (e.g., nasogastric, gastrostomy, jejunostomy) feeding • Special diets (e.g., fasting (intermittent or short-term), calorie restriction, ketogenic, Mediterranean diet, high calorie, high protein) • Supplements • Total parenteral therapy • Nutrition counseling Combined nutrition interventions (e.g., nutrition counseling with nutrition therapy)	Nutrition interventions under the supervision of a nutrition professional (e.g., dietitian, nutritionist, or other licensed clinicians) • Diet or nutrition therapy (via oral or enteral (e.g. nasogastric, gastrostomy, jejunostomy) feeding • Special diets (e.g., fasting (intermittent or short-term), calorie restriction, ketogenic, Mediterranean diet, high calorie, high protein) • Supplements • Total parenteral therapy • Nutrition counseling Combined nutrition interventions (e.g., nutrition counseling with nutrition therapy)	Nutrition interventions under the supervision of a nutrition professional (e.g., dietitian, nutritionist, or other licensed clinicians) • Diet or nutrition therapy (via oral or enteral (e.g. nasogastric, gastrostomy, jejunostomy) feeding • Special diets (e.g., fasting (intermittent or short-term), calorie restriction, ketogenic, Mediterranean diet, high calorie, high protein) • Supplements • Total parenteral therapy • Nutrition counseling Combined nutrition interventions (e.g., nutrition counseling with nutrition therapy)	Nutrition interventions intended for weight loss (includes both PNIs and NIDTs)
Comparators	Standard of care vs. PNIs or PNIs vs. PNIs	Standard of care vs. NIDTs, NIDT vs. NIDT, or PNIs vs. NIDTs	Standard of care vs. PNIs or NIDTs, NIDTs vs. NIDTs, PNIs vs. PNIs, PNIs vs. NIDTs	Standard of care vs. PNIs or NIDTs, NIDTs vs. NIDTs, PNIs vs. PNIs, PNIs vs. NIDTs

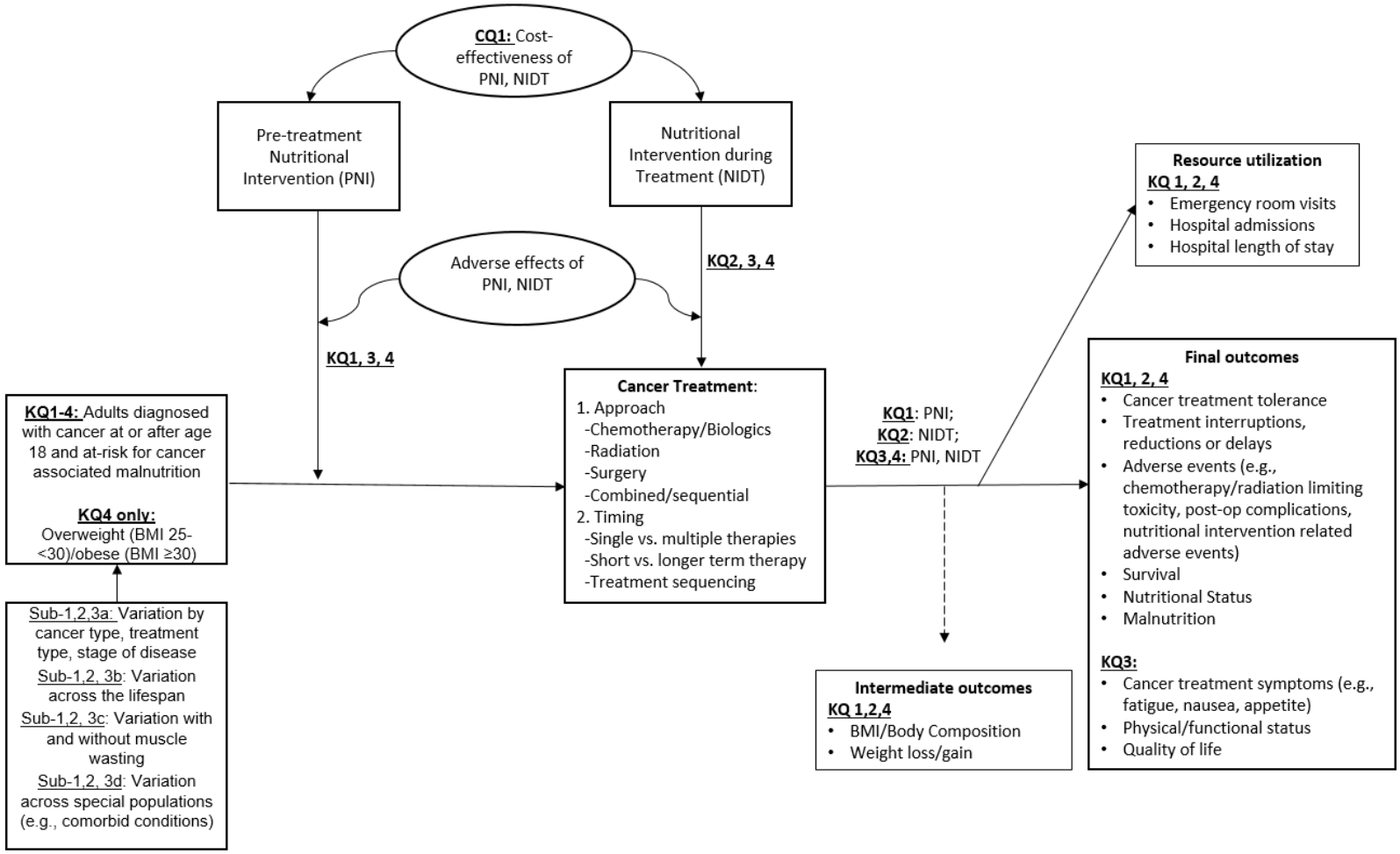
Element	KQ1: Pre-Treatment Nutrition Interventions)	KQ2: Nutrition Interventions During Treatment	KQ3: Pre- or During Treatment Nutrition Interventions and Patient-Centered Outcomes	KQ4: Weight Loss in Overweight/Obese Adults With Cancer
Outcomes	**Intermediate Outcomes** BMI, Body composition, Weight (loss, gain) **Final Outcomes** Cancer treatment tolerance: treatment interruptions, reductions, or delays Hospital utilizations: ER visits, Admissions, Length of hospital stay Adverse events: • Chemotherapy /radiation therapy limiting toxicity • Post-op complication • NI-related AEs • Unintended harms Survival: Nutrition status Malnutrition (underweight, wasting, overweight)	**Intermediate Outcomes** BMI, Body composition, Weight (loss, gain) **Final Outcomes** Cancer treatment tolerance: treatment interruptions, reductions, or delays Hospital utilizations: ER visits, Admissions, Length of hospital stay Adverse events: • Chemotherapy /radiation therapy limiting toxicity • Post-op complication • NI-related AEs • Unintended harms Survival: Nutrition status Malnutrition (underweight, wasting, overweight)	Fatigue, nausea and vomiting, appetite, physical/functional status (e.g., frailty) Quality of life	**Intermediate Outcomes** BMI, body composition, weight (loss, gain) **Final Outcomes** Cancer treatment tolerance: treatment interruptions, reductions, or delays Hospital utilizations: ER visits Admissions, Length of hospital stay Adverse events: • Chemotherapy/radiation therapy limiting toxicity • Post-op complication • NI-related AEs • Unintended harms Survival: Nutrition Status Malnutrition (underweight, wasting, overweight)
Timing	Nutrition interventions delivered pre-cancer treatment (KQ1, KQ3, KQ4) and during cancer treatment (KQ2, KQ3, KQ4)	Nutrition interventions delivered pre-cancer treatment (KQ1, KQ3, KQ4) and during cancer treatment (KQ2, KQ3, KQ4)	Nutrition interventions delivered pre-cancer treatment (KQ1, KQ3, KQ4) and during cancer treatment (KQ2, KQ3, KQ4)	Nutrition interventions delivered pre-cancer treatment (KQ1, KQ3, KQ4) and during cancer treatment (KQ2, KQ3, KQ4)
Setting	Outpatient oncology care, ambulatory care, cancer treatment centers, inpatient, home-based, hospice, telemedicine	Outpatient oncology care, ambulatory care, cancer treatment centers, inpatient, home-based, hospice, telemedicine	Outpatient oncology care, ambulatory care, cancer treatment centers, inpatient, home-based, hospice, telemedicine	Outpatient oncology care, ambulatory care, cancer treatment centers, inpatient, home-based, hospice, telemedicine

Abbreviations: AE=adverse event; KQ=Key Question; BMI=body mass index; ER=emergency room; NI=nutrition intervention; NIDT=nutrition intervention during treatment; PICOTS=population, intervention, comparator, outcomes, timing, setting; PNI=pre-treatment nutrition intervention.

Analytic Framework

Figure 2.1 shows a visual representation of the analytic framework for the KQs, illustrating the relationship of interventions and outcomes.

Figure 2.1. Analytic framework



Abbreviations: BMI=body mass index; CQ = Contextual Question; KQ=Key Question; NIDT: Nutrition intervention during treatment: PNI: Pre-treatment nutrition intervention.

Search Strategy and Study Selection

We selected studies based on the population, intervention, comparator, outcome, timing, and setting (PICOTS) framework outlined in Table 2.1 if they were published in English in a peer-reviewed journal. We evaluated any randomized controlled trial that examined nutrition interventions delivered to adults prior to or during cancer treatment for relevance to either the Key Questions or the Contextual Question (CQ). To identify the literature with the highest likelihood of having statistical power to detect an effect from a nutrition intervention, we further limited included studies to those randomizing at least 50 participants (i.e., approximately 25 individuals per arm). Studies that described the cost or value (e.g., cost-effectiveness, cost-benefit) of nutrition interventions were considered eligible for the CQ. All studies identified as potentially eligible for the review were potentially eligible for the CQ as well.

The methods for this systematic review followed the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview) and the PRISMA[19]and *PRISMA-Searching*[20] reporting guidelines. We conducted a comprehensive literature search in July 2022, searching MEDLINE (Ovid), Embase (Ovid), and Cochrane Central Register of Controlled Trials (Wiley). The search included literature published from 2000 through July 2022 to encompass contemporary cancer treatments (e.g., intensity modulated radiation therapy that allowed for better sparing of normal tissues and reduction in toxicity emerged in the late 1990s and rapidly advanced in use in early 2000s). See Appendix A for full details.

We reviewed bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. Search results were downloaded to PICO Portal™,[21] an online systematic review platform, for screening. Two trained, independent investigators reviewed titles and abstracts for identified studies meeting PICOTS framework and study selection criteria. Two reviewers independently performed full text screening to determine whether studies met inclusion criteria. Differences in screening decisions were resolved by consultation between reviewers, and, if necessary, consultation with a third investigator. All citations deemed appropriate for inclusion through title and abstract review by both reviewers were then examined at full text. We documented inclusion and exclusion status of citations, noting reasons for exclusion (see Appendix B for list of excluded studies). Throughout the screening process, members of the review team met regularly to discuss training material and issues as they arose to ensure that inclusion criteria were consistently applied. For our contextual question, we evaluated all studies included in KQ 1-4 that included discussions of the cost and effectiveness of the intervention. We supplemented these studies with a grey literature search (see Appendix A for search strategy) of systematic reviews of the cost or value of nutrition interventions in oncology and published studies from national nutrition (e.g., American Society for Parenteral and Enteral Nutrition) and oncology groups (e.g., Oncology Nutrition Dietetic Practice Group of the Academy of Nutrition and Dietetics). We defined cost-effectiveness as the cost of intervention relative to another intervention (or status quo) to gain a unit of health outcome such as a life year gained or death prevented.[22] Cost-benefit analyses evaluated the net benefits (minus the costs) of an intervention.[23]

We conducted additional grey literature searches using the Google search engine to identify relevant completed and ongoing studies, outcomes, and analyses not reported in the published literature and to inform future research needs.

Assessing Methodological Risk of Bias of Individual Studies

Based on AHRQ guidance,[24] two independent reviewers assessed risk of bias on a subset of eligible studies. This subset of studies was those that had a relatively large number of studies within an intervention/cancer type. Our threshold of 10 studies within a specific intervention/cancer type resulted in dietary supplements and nutrition support for gastrointestinal cancers being a frequent category for risk of bias assessment. (See Data Synthesis section below for descriptions of intervention categories.) We then extended risk of bias to dietary supplements and nutrition support for gastrointestinal cancers across all KQs to ensure the majority of studies of nutrition interventions in the most common cancer type were assessed for risk of bias (See Table 4.1 for an overview of studies where risk of bias was assessed). Any discrepancies in overall risk of bias assessments were resolved through reviewer discussion. We classified overall risk of bias for each study as low, moderate, or high, based on the collective risk of bias inherent in each domain, and confidence that the results are believable given the study's limitations. Types of potential bias we evaluated for each eligible study included:

- Selection bias: adequacy of randomization method
- Attrition bias: loss to follow up, both overall and differentially between treatment groups
- Detection bias: outcome assessor masking, outcome measurement quality
- Performance bias: intention to treat analysis, adjustment for potential confounding variables, participant masking to treatment assignment
- Reporting bias: selective reporting of outcomes

Data Abstraction and Data Management

Studies meeting inclusion criteria were distributed among investigators for data extraction. For all study designs, these data fields included author, year of publication, PubMed Identification Number, study design, population (including patient characteristics of interest noted in Table 2.1), intervention(s), study follow up, and setting. As outlined above, we assessed a subset of eligible studies addressing KQ 1–4 for risk of bias. For studies with low- or medium-risk-of-bias, we abstracted information on intervention duration, comparisons, outcomes, and funder. We provide a detailed evidence map/summary of studies deemed eligible but judged high risk of bias in Appendixes C–G. References for Appendixes C–G are provided in Appendix H.

Data Synthesis

Due to the significant heterogeneity of intervention types, comparators, outcomes, and timing evaluated within KQs, meta-analysis was generally not feasible or appropriate. Further, the number of eligible studies was much larger than anticipated yet distributed across a wide range of interventions and cancer types. We therefore determined that an evidence map synthesis would be most feasible and valuable. We organized the results by KQ, then broadly by type of nutrition intervention and type of cancer. As the mechanisms for the effect of nutrition interventions for preventing and treating the negative outcomes of cancer and cancer treatment may vary by cancer stage and the treatment itself, we also report these characteristics as well. As outlined above in the Report Organization, some interventions were not exclusively delivered prior to cancer treatment (KQ1, Chapter 5) or after cancer treatment began (KQ2, Chapter 7).

Therefore, chapter 6 separately presents studies of interventions that were initiated prior to and continued after cancer treatment began (i.e., spans KQs 1 and 2).

We grouped nutrition interventions into six broad categories (Table 2.2). Given the lack of a recognized classification system for grouping or describing non-pharmacologic nutrition interventions, we grouped studies into single intervention types based on the content and intent of the intervention and the intended audience, using taxonomies and definitions where available. We acknowledge that our categorization scheme represents broad definitions and that our assignments may not be precise. Classification, particularly within an intervention type, presented challenges due to the extreme heterogeneity of interventions and comparison populations. Therefore, we grouped studies best aligned with other studies in the same intervention type that assessed, to the best extent possible, similar intervention components (e.g., a single dietary supplement). Given the volume and heterogeneity of evidence, this strategy helped us to adequately synthesize and interpret results.

Table 2.2. Intervention categories and descriptions

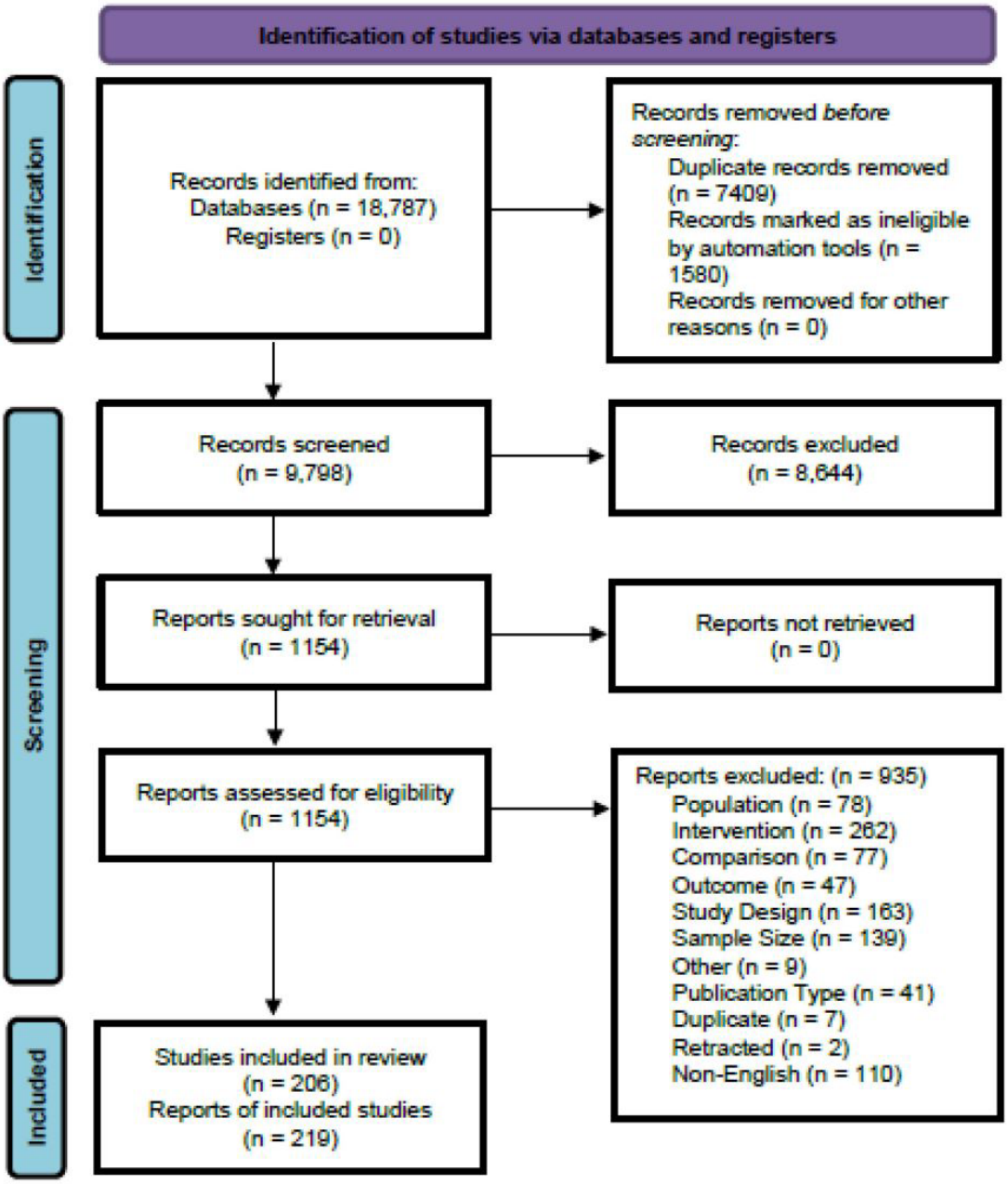
Intervention Category	Description
Nutrition Counseling	Nutrition counseling involves an individualized nutrition assessment followed by personalized care of nutrition and diet-related needs with the goal of achieving and maintaining optimal nutrition status across the continuum of care.
Dietary Supplements	Dietary Supplements include products (e.g., added arginine, glutamine, fish oil) containing one or more ingredients meant to supplement the diet for improved nutrition status, but were not meant to replace calories. Vitamins, minerals and antioxidants were not included.
Special Diets	Special diets include the use of defined nutrition plans or approaches such as fasting (intermittent or short term), calorie restriction, ketogenic, Mediterranean, high calorie, or high protein diets to support cancer care.
Route or Timing of Nutrition Interventions	Route or timing interventions involve testing only the route (e.g., PEG tube, enteral feeding) or timing (e.g., initiation or duration) of nutrition interventions with similar nutrition contents.
Nutrition Support Including Oral Nutrition Supplements	Nutrition Support interventions involve the use of total parenteral nutrition, enteral nutrition (tube feeding), and oral nutrition supplements (e.g., Ensure®, Boost®, immunonutrition (oral nutrition supplements that include a set of nutrients meant to have an effect of the immune system[25])) to maintain or improve nutrition status.
Multi-Component Interventions	Multi-component interventions involve multiple strategies for nutrition interventions, such as counseling plus use of dietary supplements.

For each intervention type, we present results in two general sections: Eligible Studies and Description of Interventions. To provide a deeper description of the literature, we give two further results sections for those intervention/cancer type groups with a relatively larger number of studies. The first additional section describes the assessed risk of bias for eligible studies. For studies with low and medium risk of bias, we then provide an additional section that qualitatively describes the reported directionality of outcomes. We use arrows for directionality to indicate, for each outcome comparison, whether an intervention shows a benefit, a harm, or neither benefit nor harm.

Chapter 3. Search Results

We list all studies excluded at full text screening, by exclusion category, in Appendix B. See Figure 3.1 for details of the screening process.

Figure 3.1. Literature flow diagram



Based on a comprehensive literature search conducted July 2022, we identified 9,798 unique references. Based on title and abstract review, we excluded 8,644 references not relevant to Key Questions 1– 4. Of the remaining 1,154 references, 206 studies from 219 publications were considered eligible after full text review.

We organized the results by Key Question, then broadly by type of nutrition intervention and type of cancer. Table 3.1 provides an overview of the eligible literature set by nutrition intervention and Key Question. We describe studies for which risk of bias was assessed in Chapter 4, Table 4.1.

Table 3.1. Identified unique included studies by intervention and Key Question

Location	Intervention	Total
Chapter 5 Nutrition Interventions Prior to Cancer Treatment (KQ1)	Nutrition Counseling	0
	Dietary Supplements	5
	Special Diets	0
	Route or Timing of Nutrition Interventions	0
	Nutrition Support Including Oral Nutrition Supplements	15
	Multi-Component Interventions	0
	Total	**20**
Chapter 6 Nutrition Interventions Prior to and Including the Initiation of Cancer Treatment (Spans KQ 1 and 2)	Nutrition Counseling	0
	Dietary Supplements	15
	Special Diets	0
	Route or Timing of Nutrition Interventions	9
	Nutrition Support Including Oral Nutrition Supplements	13
	Multi-Component Interventions	1
	Total	**38**
Chapter 7 Nutrition Interventions after Treatment Began (KQ2)	Nutrition Counseling	15
	Dietary Supplements	34
	Special Diets	8
	Route or Timing of Nutrition Interventions	31
	Nutrition Support Including Oral Nutrition Supplements	43
	Multi-Component Interventions	10
	Total	**141**
Chapter 8 Effect of Nutrition Interventions on Symptoms (KQ3)	Nutrition Counseling	12
	Dietary Supplements	10
	Special Diets	10
	Route or Timing of Nutrition Interventions	8
	Nutrition Support Including Oral Nutrition Supplements	32
	Multi-Component Interventions	7
	Total	**79**
Chapter 9 Effect of Nutrition Interventions on Weight Loss (KQ4)	Nutrition Counseling	0
	Dietary Supplements	0
	Special Diets	4
	Route or Timing of Nutrition Interventions	0
	Nutrition Support Including Oral Nutrition Supplements	0
	Multi-Component Interventions	0
	Total	**4**

Note: Numbers of totals and numbers of included studies are not mutually exclusive. Studies addressing KQ3 could also address KQ1, KQ2 or span KQ1 and 2. includes a total of 206 unique studies across 219 publications.
Abbreviation: KQ=Key Question.

Chapter 4. Overview of Nutrition Interventions

Key Points

- Two decades of randomized trial evidence across 206 studies of nutrition interventions for adults prior to and/or during cancer treatment focused on use of dietary supplements, nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions within gastrointestinal and head and neck cancers.
- Studies focused on evaluating changes in body weight/composition, adverse events, length of hospital stay, and quality of life.
- Among studies with a high volume of literature (n=114), which predominately examined dietary supplements and nutrition support in patients with gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias and 49 percent (n=56) high risk of bias (lower quality).
- Despite a large volume of studies evaluating nutrition interventions and outcomes of interest across Key Questions (KQs), heterogeneity was high across study populations, interventions, and outcomes (measure definitions, timing of measurements), even within nutrition intervention categories, making meta-analysis infeasible.

Intervention Type, Outcomes, and Risk of Bias

This chapter provides an evidence map of the KQ 1–4 included studies. Here we present interventions across KQs in aggregate to provide a broad evidence map of the types of interventions studied by KQ and cancer type (Table 4.1). Among this literature, the highest volume of studies focused on gastrointestinal cancers; head and neck cancers were second most common. Interventions focused mainly on use of dietary supplements, nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions. Few studies examined nutrition counseling, use of special diets, or multi-component interventions. Also, few studies evaluated nutrition interventions aimed at body weight loss (KQ 4, n=4) among cancer patients who were overweight or obese. Within each KQ and nutrition intervention type, we found significant heterogeneity of study populations, timing, and duration of the interventions, as well as the interventions themselves (details are provided by KQ in Chapters 5-9).

Table 4.1. Identified unique included studies by nutrition intervention and cancer type across Key Questions

Location	Intervention	Head and Neck Cancer	Gastrointestinal Cancer	Multiple Cancers	Other Cancer Types*	Total†
Chapter 5 Nutrition Interventions Prior to Cancer Treatment (KQ1)	Nutrition Counseling	0	0	0	0	0
	Dietary Supplements	1	**2***	0	2	5
	Special Diets	0	0	0	0	0
	Route or Timing of Nutrition Interventions	0	0	0	0	0
	Nutrition Support Including Oral Nutrition Supplements	0	**15***	0	0	15
	Multi-Component Interventions	0	0	0	0	0
	Total	-	-	-	-	**20**

Location	Intervention	Head and Neck Cancer	Gastrointestinal Cancer	Multiple Cancers	Other Cancer Types*	Total†
Chapter 6 Nutrition Interventions Prior to and Including the Initiation of Cancer Treatment (Spans KQ 1 and 2)	Nutrition Counseling	0	0	0	0	0
	Dietary Supplements	2	**10***	2	1	15
	Special Diets	0	0	0	0	0
	Route or Timing of Nutrition Interventions	2	6	1	0	9
	Nutrition Support Including Oral Nutrition Supplements	1	**10***	0	2	13
	Multi-Component Interventions	0	0	1	0	1
	Total	-	-	-	-	**38**
Chapter 7 Nutrition Interventions after Treatment Began (KQ2)	Nutrition Counseling	3	4	6	2	15
	Dietary Supplements	**10***	**16***	3	5	34
	Special Diets	0	1	2	5	8
	Route or Timing of Nutrition Interventions	4	**24***	1	2	31
	Nutrition Support Including Oral Nutrition Supplements	4	**27***	4	8	43
	Multi-Component Interventions	2	2	2	4	10
	Total	-	-	-	-	**141**
Chapter 8 Effect of Nutrition Interventions on Symptoms (KQ3)	Nutrition Counseling	1	4	4	3	12
	Dietary Supplements	1	**5***	3	1	10
	Special Diets	0	1	2	7	10
	Route or Timing of Nutrition Interventions	2	4	1	1	8
	Nutrition Support Including Oral Nutrition Supplements	5	**20***	3	4	32
	Multi-Component Interventions	2	0	3	2	7
	Total	-	-	-	-	**79**
Chapter 9 Effect of Nutrition Interventions on Weight Loss (KQ4)	Nutrition Counseling	0	0	0	0	0
	Dietary Supplements	0	0	0	0	0
	Special Diets	0	0	0	4	4
	Route or Timing of Nutrition Interventions	0	0	0	0	0
	Nutrition Support Including Oral Nutrition Supplements	0	0	0	0	0
	Multi-Component Interventions	0	0	0	0	0
	Total	-	-	-	-	**4**

Note: Numbers of totals and numbers of included studies are not mutually exclusive. Studies addressing KQ3 could also address KQ1, KQ2, or span KQ 1 and 2. Includes a total of 206 unique studies across 219 publications.
Abbreviations: KQ= Key Question; - = Not Applicable.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer;
†Indicates studies in which risk of bias was assessed.

Outcomes evaluated also varied significantly across KQs. Table 4.2 provides a summary of the outcomes evaluated. For nutrition interventions prior to cancer treatment (KQ1), studies most commonly evaluated intermediate outcomes such as changes in body weight/composition changes or nutrition status, and final outcomes such as adverse events and length of hospital stay.

Studies examining nutrition interventions prior to and including the initiation of cancer treatment (spans KQs 1 and 2) most commonly evaluated body weight/composition changes as intermediate outcomes and adverse events, survival, and length of hospital stay as final outcomes. Studies evaluating nutrition interventions during cancer treatment (KQ2) looked at a wide range of outcomes, most commonly evaluating adverse events, followed by body weight/composition changes and length of hospital stay. Evaluation of the effects of nutrition interventions on cancer and treatment-related symptoms (KQ3) most commonly evaluated quality of life outcomes followed by changes in reported symptoms. Few studies evaluated the impact of nutrition interventions on readmissions/emergency room visits or changes in treatment tolerance. Although a large volume of studies evaluated outcomes of interest across KQs, significant heterogeneity among measure definitions, timing of measurements, and populations evaluated made aggregation or meta-analyses less feasible.

Table 4.2. Number of studies evaluating outcomes by Key Question*

Location	Intervention	Body Weight/Composition	Changes in Nutrition Status	AEs	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms*	Functional Status
Chapter 5 Nutrition Interventions Prior to Cancer Treatment (KQ1)	Nutrition Counseling	0	0	0	0	0	0	-	-	-	-
	Dietary Supplements	2	1	2	0	2	1	-	-	-	-
	Special Diets	0	0	0	0	0	0	-	-	-	-
	Route or Timing of Nutrition Intervention	0	0	0	0	0	0	-	-	-	-
	Nutrition Support Including Oral Nutrition Supplement	7	4	12	2	1	10	-	-	-	-
	Multi-Component Interventions	0	0	0	0	0	0	-	-	-	-
	Total (20 studies)	9	5	14	2	3	11	-	-	-	-
Chapter 6 Nutrition Interventions Prior to and Including the Initiation of Cancer Treatment (Spans KQ 1 and 2)	Nutrition Counseling	0	0	0	0	0	0	-	-	-	-
	Dietary Supplements	9	3	13	2	9	7	-	-	-	-
	Special Diets	0	0	0	0	0	0	-	-	-	-
	Route or Timing of Nutrition Interventions	4	2	6	1	1	5	-	-	-	-
	Nutrition Support Including Oral Nutrition Supplements	4	0	12	3	6	9	-	-	-	-
	Multi-Component Interventions	0	0	0	0	1	0	-	-	-	-

Location	Intervention	Body Weight/Composition	Changes in Nutrition Status	AEs	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms*	Functional Status
	Total (38 studies)	17	5	31	6	17	21	-	-	-	-
Chapter 7 Nutrition Interventions after Treatment Began (KQ2)	Nutrition Counseling	12	9	6	1	6	1	-	-	-	-
	Dietary Supplements	20	5	26	3	12	18	-	-	-	-
	Special Diets	4	0	3	0	2	1	-	-	-	-
	Route or Timing of Nutrition Interventions	12	6	28	2	10	22	-	-	-	-
	Nutrition Support Including Oral Nutrition Supplements	26	14	32	4	12	13	-	-	-	-
	Multi-Component Interventions	7	5	3	1	3	2	-	-	-	-
	Total (141 studies)	81	39	98	11	45	57	-	-	-	-
Chapter 8 Effect of Nutrition Interventions on Symptoms	Nutrition Counseling	-	-	-	-	-	-	3	9	6	6
	Dietary Supplements	-	-	-	-	-	-	2	7	5	2
	Special Diets	-	-	-	-	-	-	0	7	7	3
	Route or Timing of Nutrition Interventions	-	-	-	-	-	-	2	6	1	1
	Nutrition Support Including Oral Nutrition Supplements	-	-	-	-	-	-	7	20	13	9
	Multi-Component Interventions	-	-	-	-	-	-	0	6	3	2

Location	Intervention	Body Weight/Composition	Changes in Nutrition Status	AEs	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms*	Functional Status
	Total (79 studies)	-	-	-	-	-	-	14	55	35	23
Chapter 9 Effect of Nutrition Interventions on Weight Loss (KQ4)	Nutrition Counseling	0	0	0	0	0	-	-	-	-	
	Dietary Supplements	0	0	0	0	0	-	-	-	-	
	Special Diets	4	0	0	0	0	-	-	-	-	
	Route or Timing of Nutrition Interventions	0	0	0	0	0	-	-	-	-	
	Nutrition Support Including Oral Nutrition Supplements	0	0	0	0	0	-	-	-	-	
	Multi-Component Interventions	0	0	0	0	0	-	-	-	-	
	Total (4 studies)	4	0	0	0	0	-	-	-	-	

Note: Studies may evaluate more than one outcome.
Abbreviations: AE= adverse events; LOS=Length of hospital stay; QOL=Quality of Life; - = Not Applicable.
*Symptoms may include cancer or cancer treatment related symptoms such as fatigue, nausea and vomiting, and appetite.

As detailed in our methods, we assessed risk of bias for studies within a higher volume of nutrition intervention literature (Table 4.3). These interventions included studies predominantly evaluating dietary supplements, nutrition support (including oral nutrition supplements), and route or timing of nutrition interventions. Among these studies, we assessed the literature as having mostly moderate to high risk of bias, with 49 (n=56) percent of studies rated as high. Only 11 percent (n=12) of studies were rated as low risk of bias.

Table 4.3. Overview of risk of bias assessment

Location	Intervention	Head and Neck Cancer	Gastrointestinal Cancer	Multiple Cancers	Other Cancer Types*
Chapter 5 Nutrition Interventions Prior to Cancer Treatment (KQ1)	Nutrition Counseling	-	-	-	-
	Dietary Supplements	-	2 High (N=2)	-	-
	Special Diets	-	-	-	-
	Route or Timing of Nutrition Interventions	-	-	-	-
	Nutrition Support Including Oral Nutrition Supplements	-	2 Low 6 Medium 7 High (N=15)	-	-
	Multi-Component Interventions	-	-	-	-
Chapter 6 Nutrition Interventions Prior to and Including the Initiation of Cancer Treatment (Spans KQ 1 and 2)	Nutrition Counseling	-	-	-	-
	Dietary Supplements	-	4 Medium 6 High (N=10)	-	-
	Special Diets	-	-	-	-
	Route or Timing of Nutrition Interventions	-	-	-	-
	Nutrition Support Including Oral Nutrition Supplements	-	2 Low 4 Medium 4 High (N=10)	-	-
	Multi-Component Interventions	-	-	-	-
Chapter 7 Nutrition Interventions after Treatment Began (KQ2)	Nutrition Counseling	-	-	-	-
	Dietary Supplements	6 Medium 4 High (N=10)	4 Low 8 Medium 4 High (N=16)	-	-
	Special Diets	-	-	-	-
	Route or Timing of Nutrition Interventions	-	1 Low 10 Medium 13 High (N=24)	-	-
	Nutrition Support Including Oral Nutrition Supplements	-	3 Low 8 Medium 16 High (N=27)	-	-
	Multi-Component Interventions	-	-	-	-
Chapter 8 Effect of Nutrition Interventions on	Nutrition Counseling	-	-	-	-
	Dietary Supplements	-	3 Medium 2 High (N=5)	-	-
	Special Diets	-	-	-	-

Location	Intervention	Head and Neck Cancer	Gastrointestinal Cancer	Multiple Cancers	Other Cancer Types*
Symptoms (KQ3)#	Route or Timing of Nutrition Interventions	-	-	-	-
	Nutrition (nutrition support)	-	5 Low 4 Medium 11 High (N=20)	-	-
	Multi-Component Interventions	-	-	-	-
Chapter 9 Effect of Nutrition Interventions on Weight Loss (KQ4)	Nutrition Counseling	-	-	-	-
	Dietary Supplements	-	-	-	-
	Special Diets	-	-	-	-
	Route or Timing of Nutrition Interventions	-	-	-	-
	Nutrition Support Including Oral Nutrition Supplements	-	-	-	-
	Multi-Component Interventions	-	-	-	-

Note: Numbers of totals and numbers of included studies are not mutually exclusive. Studies addressing KQ3 could also address KQ1, KQ2 or span KQ1 and 2.
Abbreviations: - = Not Applicable; KQ=Key Question; N=number.

* Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Chapter 5. Nutrition Interventions Prior to Cancer Treatment

Key Points

- Studies of nutrition interventions prior to cancer treatment included use of dietary supplements and nutrition support mostly among gastrointestinal cancer populations in the inpatient surgical setting and outpatient settings.
- Studies focused on evaluating changes in body weight/composition, changes in nutrition status, adverse events, survival, and length of hospital stay.
- Of studies assessed for risk of bias, all dietary supplement studies and 47 (7/15) percent of nutrition support studies were high risk of bias (poor quality).
- Among eight low- or medium-risk-of-bias studies in nutrition support, studies reported mixed results on development of complications, improvements in body weight loss, and length of hospital stay
- Studies showed high heterogeneity across study populations, interventions, and outcomes so meta-analysis was not feasible.

Overview

This chapter includes studies that addressed Key Question (KQ) 1 and examined nutrition interventions that were only delivered prior to the initiation of cancer treatment. Chapter 6 separately presents studies of interventions that were initiated prior to and continued during cancer treatment (KQs 1 and 2). In order to briefly discuss what has been examined for each intervention type, we present results in two general sections: Eligible Studies and Description of Interventions. We assessed risk of bias for nutrition intervention/cancer types with a higher volume of studies. This allowed us to identify the greatest amount of lower-risk of bias evidence concentrated by specific nutrition interventions by cancer type. The number of studies for which we assessed risk of bias is indicated in Table 5.1. For interventions with low- to medium-risk-of-bias studies, we note reported outcome directionality the end of the chapter. Detailed information on all eligible studies can be found in Appendix C.

For KQ1, we identified 20 unique studies that examined nutrition interventions prior to the initiation of cancer treatment. Studies examined the use of dietary supplements (n=5) and nutrition support (n=15) (Table 5.1). No studies examined the use of nutrition counseling alone, or the route or timing of nutrition interventions, special diets, or multicomponent interventions. Table 5.1 summarizes the characteristics of the literature set.

Table 5.1. Studies examining use of nutrition interventions prior to cancer treatment, stratified by intervention and cancer type* (KQ1)

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types†	Total
Nutrition Counseling	0	0	0	0	0
Dietary Supplements	1	**2***	0	2	5
Special Diets	0	0	0	0	0
Route or Timing of Nutrition Interventions	0	0	0	0	0
Nutrition Support Including Oral Nutrition Supplements	0	**15***	0	0	15

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types†	Total
Multi-Component Interventions	0	0	0	0	0
Total	-	-	-	-	20

Abbreviations: KQ= Key Question; - = Not applicable.
*Risk of bias was performed.
†Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Dietary Supplements

Eligible Studies

Table 5.2 summarizes the characteristics of the literature set. We identified five unique small studies examining dietary supplements used prior to cancer treatment.[26-30] All enrolled 100 or fewer individuals, and primarily assessed the impact of dietary supplements on clinical laboratory outcomes such as immune response,[27, 28] inflammatory profiles,[28] or components of a metabolic panel.[29, 30] The primary outcome of the study incorporating head and neck cancer patients was prevention of severe oral mucositis.[26] Dietary supplements were prescribed by a dietitian/nutritionist in two studies, where the primary cancer treatment was chemotherapy alone.[26, 28] Appendix C provides detailed evidence tables.

Table 5.2. Basic characteristics of studies of nutrition interventions prior to cancer treatment: dietary supplements

Characteristics	Information
Total Included Studies	5 Studies
Study Sample Size	3 50-75 2 76-100
Cancer Type	1 Head & Neck 2 Gastrointestinal 2 Other cancer types*
Intervention Delivery Setting	2 Inpatient 2 Outpatient 1 Not reported
Dominant Cancer Treatment Type of Participants	3 Surgery alone 2 Chemotherapy alone
Limited to Malnourished Patients	5 No
Malnourishment Screening Tool Used	1 Multiple tools/metrics 2 Other tool/metric 2 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 1 Other 1 Physician 1 Not reported
Route of Administration	3 Oral 1 Parenteral 1 Not reported
Geographic Region of Intervention	1 Asia 2 Europe 2 Other
% of Participants with Stage IV Disease	2 <10% 1 >50% 2 Not reported
% Female Participants	2 0-25% 2 26-50% 1 76-100%

Characteristics	Information
Mean Age of Participants	4 50-64 1 Not reported
Outcomes Evaluated†	2 Body weight or composition changes 1 Changes in nutrition status 2 Adverse events 2 Survival 1 Length of stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
† Studies may evaluate multiple outcomes.

Description of Interventions

One study compared parenteral fish oil lipid emulsion versus lipid emulsions rich in triglycerides prior to gastrointestinal cancer surgery.[27] Another study compared an oral nutrition formula enriched with omega-3 fatty acids versus a standard oral nutrition formula for gastric cancer.[28] A third study compared an immune modulating formula enriched with arginine, omega-3 fatty acids, and nucleotides versus a normal diet for lung cancer.[29] Another study compared an oral immunonutrition formula with fatty acids, arginine, fiber, and nucleotides versus a standard enteral formula in head and neck cancer patients.[26] A final study compared preoperative oral carbohydrate loading versus standard fasting prior to breast cancer surgery.[30] These studies were not U.S.-based, with two conducted in Brazil,[27, 28] one in Norway,[30] one in Thailand,[26] and one in Turkey.[29] Overall, studies differed widely in type of dietary supplements administered, route of administration, and control populations.

Nutrition Support Including Oral Nutrition Supplements

Eligible Studies

Table 5.3 summarizes the characteristics of the literature set. We identified 15 unique studies examining nutrition support interventions prior to cancer treatment.[31-45] All interventions were delivered among patients with gastrointestinal cancer. Eight studies had sample sizes over 100. The primary aims of these studies varied and include adverse events or postoperative complications,[31, 32, 38] body weight or composition changes,[37] changes in nutrition status,[42-45] immune function,[43, 44] intraoperative core temperature during surgery,[34] quality of life,[37] feeding intolerance rate,[35] physical status,[42] and self-sufficiency.[42] Five studies did not a report a specific primary aim. [33, 36, 39-41] Most studies investigated the effect of nutrition supplementation before cancer treatment on length of stay[31-34, 36-42, 44, 45] and adverse events or complications.[31-35, 38, 39, 41-44] Appendix C provides detailed evidence tables.

Table 5.3. Basic characteristics of studies of nutrition interventions prior to cancer treatment: nutrition support including oral nutrition supplements

Characteristics	Information
Total Included Studies	15 Studies
Study Sample Size	6 50-75 1 76-100 8 >100
Cancer Type	15 Gastrointestinal

Characteristics	Information
Intervention Delivery Setting	10 Inpatient 2 Outpatient 1 Multiple settings 1 Other 1 Not reported
Dominant Cancer Treatment Type of Participants	13 Surgery alone 2 Multiple therapies
Limited to Malnourished Patients	1 Yes 14 No
Malnourishment Screening Tool Used	5 Nutrition Risk Screening NRS-2002 5 Other tool/metric 5 Not reported
Provider Prescribing or Delivering the Intervention	3 Dietitian/nutritionist 1 Multiple 11 Not reported
Route of Administration	12 Oral 1 Parenteral 2 Enteral
Geographic Region of Intervention	8 Asia 6 Europe 1 North America
% of Participants with Stage IV Disease	6 <10% 1 20-29% 8 Not reported
% Female Participants	2 ≤25% 11 26-50% 2 51-75%
Mean Age of Participants	8 50-64 6 65+ 1 Not reported
Outcomes Evaluated*	7 Body weight or composition changes 4 Changes in nutrition status 12 Adverse events 2 Readmissions or emergency room visits 1 Survival 10 Length of stay

*Studies may evaluate multiple outcomes.

Description of Interventions

Most interventions were delivered preoperatively in a surgical setting. One study compared the use of daily oral supplementation with Fortisip® oral nutrition support and dietary advice for a minimum of 10 days prior to surgery for colorectal cancer versus dietary advice alone.[32] The same group then conducted a larger trial comparing daily oral supplementation with Fortsip Compact® along with dietary advice versus dietary advice alone before surgery in patients with colorectal cancer.[31]

Three studies specifically looked at immunonutrition. One compared oral whole immunonutrition (IMPACT Advanced Recovery) versus no additional supplementation in adults with locally advanced pancreatic adenocarcinoma before irreversible electroporation.[39] The second compared enteral immunonutrition (IMPACT) versus standard enteral nutrition before elective curative surgery for patients with colorectal or gastric carcinoma.[44] The third study investigated preoperative immunonutrient-enriched supplementation (Newcare Omega®) versus normal diet in patients receiving elective colon cancer resection.[38]

Other studies were more diverse in the type of oral nutrition support across different types of gastrointestinal cancers. One study of gastrointestinal patients compared Nutricia® starting 1

week preoperatively and a short peptide-based elemental diet for nine days postoperatively via a nasogastric tube versus no preoperative use of oral nutrition supplements.[43] Another study compared preoperative, oral, hypercaloric supplementation (Nutridrink Protein®) versus a regular diet for individuals with gastrointestinal cancer.[36] A third examined peripheral intravenous nutrition on typically fasting days for patients undergoing workup for biliopancreatic masses.[37] Another study compared preoperative oral supplementation versus preoperative dietary advice for individuals undergoing surgery for gastrointestinal cancer.[35] One study compared oral nutrition combined with microbial preparations versus traditional intestinal preparation in elderly patients before radial resection of colorectal cancer.[41] A sixth study examined preoperative oral nutrition compared to no oral supplementation in patients undergoing elective resection of colorectal carcinoma.[42] The remaining study compared Nutrison Fiber® versus a routine preoperative diet in patients with Siewert II and III adenocarcinomas of esophagogastric junction after neoadjuvant chemotherapy.[45]

The final three studies examined carbohydrate-rich beverages. One compared oral supplementation with a carbohydrate-rich beverage (Arginaid Water®) versus drinking clear water before undergoing laparoscopic colon cancer surgery.[34] The second compared a carbohydrate rich beverage in the 2 days prior to surgery for colorectal cancer versus preoperative fasting.[40] Another study investigated the effects of a single-dose versus a double-dose of a 10% glucose solution prior to radical gastrectomy.[33] Overall, studies varied widely in the type of nutrition support administered, route of administration, and control populations.

Risk of Bias and Outcome Assessment

Table 5.4 summarizes risk of bias assessment. Appendix C provides risk of bias assessments by study and qualitatively describes the reported directionality of reported outcomes.

Table 5.4. Risk of bias assessment for nutrition interventions prior to cancer treatment

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types*
Nutrition Counseling	-	-	-	-
Dietary Supplements	-	2 High (N=2)	-	-
Special Diets	-	-	-	-
Route or Timing of Nutrition Interventions	-	-	-	-
Nutrition Support Including Oral Nutrition Supplements	-	2 Low 6 Medium 7 High (N=15)	-	-
Multi-Component Interventions	-	-	-	-

Note: - = risk of bias not performed.
* Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Outcomes for Dietary Supplements

Both studies were evaluated as high risk of bias (low quality) and outcomes were not evaluated.

Outcomes for Nutrition Support Including Oral Nutrition Supplements

Six of eight studies of low to medium risk of bias examined surgically treated gastrointestinal cancer patients receiving nutrition interventions in the hospital.[31, 32, 38, 40, 44 42] Study sample sizes ranged from 50 to 161. One to two studies reported on each of the following outcomes: readmissions or emergency room visits and changes in nutritional status. Seven studies reported on adverse events.[31-33, 35, 38, 42, 44] However, the studies were distributed across interventions that could not be aggregated. Studies showed mixed results for use of preoperative nutrition support. One medium-risk-of-bias study reported a benefit of preoperative oral nutrition support on reducing body weight loss and surgical site infections;[31] however, it showed no benefit on changes in nutrition status, chest infections or other complications, length of hospital stay, or survival. Another medium-risk-of-bias study showed no benefit of a preoperative oral supplement drink on complications.[32] A third study of preoperative nutrition support reported a benefit on noninfectious complications and length of hospital stay.[44] One medium-risk-of-bias study found no benefit for patients receiving a double-dose of a preoperative carbohydrate drink in adverse events, readmission or reoperation, and length of hospital stay.[33] Another medium-risk-of-bias study found that oral nutrition supplementation during the seven days before surgery reported a benefit on body weight recovery after discharge, but no changes in body weight or composition change overall, adverse events, or length of stay.[38] A low-risk-of-bias study found that preoperative oral nutrition supplementation had no effect on adverse events or hospital readmission compared to dietary advice.[35] Another medium-risk-of-bias study reported no benefit in body weight or composition, complications, or hospital stay for those that received oral nutritional supplements before surgery.[42] Finally, one low-risk-of-bias study reported that a preoperative carbohydrate drink reduced length of hospital stay.[40]

Variation in the Effects of Nutrition Interventions on Preventing Negative Outcomes

While studies enrolled individuals from multiple cancer types, treatments, and stages (KQ1a), across the lifespan (KQ1b), with varying degrees of muscle wasting (KQ1c) and in those with a range of comorbid conditions (KQ1d), no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Chapter 6. Nutrition Interventions Prior to and Including the Initiation of Cancer Treatment

Key Points

- Studies of nutrition interventions prior to and continuing after the start of cancer treatment included use of nutrition support, dietary supplements, and evaluation of the route or timing of nutrition interventions, mostly among gastrointestinal cancer populations in the inpatient surgical setting.
- Studies most commonly focused on evaluating changes in body weight/composition, adverse events, length of hospital stay, and survival, with five studies evaluating changes in nutrition status, readmissions, or emergency room visits.
- Of studies assessed for risk of bias, 60 percent (n=6/10) of dietary supplement studies and 40 percent (n=4/10) of nutrition support studies were high risk of bias (poor quality), with only two nutrition support studies assessed as low risk of bias.
- Among four medium-risk-of-bias studies in dietary supplements, studies reported mixed results on body weight changes, readmissions, length of hospital stay, development of complications, and survival.
- Two low- and four medium-risk-of-bias study of nutrition support reported mixed results, with some studies reporting a benefit and some reporting no difference in reducing adverse events, readmissions, length of hospital stay, and survival.
- Studies showed high heterogeneity across study populations, interventions, and outcomes, making meta-analysis infeasible.

Overview

This chapter includes nutrition interventions initiated prior to and continued after cancer treatment began, encompassing both Key Questions (KQs) 1 and 2. This stands in contrast to interventions delivered only prior to the initiation of cancer treatment (Chapter 5) and interventions delivered only after cancer treatment began (Chapter 7). For each intervention type, we present results in two general sections: Eligible Studies and Description of Interventions for a brief discussion of what has been examined. We assessed risk of bias for intervention/cancer types with a higher volume of studies. This allowed us to identify the greatest amount of lower risk of bias evidence concentrated according to specific nutrition interventions by cancer type. The number of studies by intervention type and cancer type for which we assessed risk of bias is indicated in Table 6.1. For interventions with low- to medium-risk-of-bias studies, we note outcome directionality at the end of the chapter. Detailed information on all eligible studies can be found in Appendix D.

We identified 38 unique studies across 42 publications that examined nutrition interventions prior to and after initiation of cancer treatment. Studies examined the use of dietary supplements (n=15), the route or timing of nutrition interventions (n=9), the use of nutrition support (n=13), and multicomponent interventions (n=1) (Table 6.1). No studies examined nutrition counseling or the use of special diets.

Table 6.1. Studies of nutrition interventions prior to and including initiation of cancer treatment, stratified by intervention type and cancer type

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types[a]	Total
Nutrition Counseling	0	0	0	0	0
Dietary Supplements	2	**10***	2	1	15
Special Diets	0	0	0	0	0
Route or Timing of Nutrition Interventions	2	6	1	0	9
Nutrition Support Including Oral Nutrition Supplements	1	**10***	0	2	13
Multi-Component Interventions	0	0	1	0	1
Total					38

*Risk of bias was performed.
[a]Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Dietary Supplements

Eligible Studies

Table 6.2 summarizes the characteristics of the literature set. We identified 15 unique studies across 16 publications examining the use of dietary supplements prior to and continued after the initiation of cancer treatment.[46-61] Most studies enrolled fewer than 100 individuals and primarily assessed the impact of the nutrition intervention on clinical laboratory outcomes such as components of a metabolic panel[46, 51] and biomarkers;[47, 49, 58, 59] however, a number of studies also assessed clinical outcomes such as complications.[48, 56-60] Others examined multiple outcomes but did not clearly state the primary intent.[50, 52-54, 61] The majority of studies were in gastrointestinal cancers. Dietary supplements were prescribed by a dietitian/nutritionist in only two studies, and the majority study populations were treated predominantly with surgery. Appendix D provides detailed evidence tables.

Table 6.2. Basic characteristics of studies of nutrition interventions prior to and including initiating cancer treatment: dietary supplements

Characteristics	Information
Total Included Studies	15 Studies
Study Sample Size	8 50-75 2 76-100 5 >100
Cancer Type	2 Head & neck 10 Gastrointestinal 2 Multiple cancers 1 Other cancer types[+]
Intervention Delivery Setting	6 Inpatient 5 Outpatient 1 Multiple settings 1 Other 2 Not reported
Dominant Cancer Treatment Type of Participants	11 Surgery alone 2 Chemotherapy alone 1 Radiation alone 1 Multiple therapies
Limited to Malnourished Patients	2 Yes 13 No

Characteristics	Information
Malnourishment Screening Tool Used	2 Malnourishment Screening Tool 1 Nutrition Risk Screening-2002 7 Other tool/metric 1 Multiple tools 4 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 3 Multiple providers 1 Nurse 2 Other 7 Not reported
Route of Administration	8 Oral 1 Parenteral 6 Enteral
Geographic Region of Intervention	9 Europe 4 Asia 1 North America 1 Other
% of Participants with Stage IV Disease	4 <10% 1 10-25% 1 25-50% 2 >50% 7 Not reported
% Female Participants	3 0-25% 9 26-50% 1 51-75% 1 76-100% 1 Not reported
Mean Age of Participants	11 50-64 4 ≥65
Outcomes Evaluated*	9 Body weight or composition changes 3 Changes in nutrition status 13 Adverse events 2 Readmissions or emergency room visits 9 Survival 7 Length of stay

*Studies may evaluate multiple outcomes. [+]Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Description of Interventions

One group of studies examined the use of a single supplement for immunonutrition (eicosapentaenoic - [EPA], omega-3 fatty acid or glutamine-enriched nutrition), but interventions varied by population and had a wide range of intervention durations around the time of cancer surgery. One study examined eicosapentaoenoic (EPA-enriched) nutrition in head and neck cancer versus standard nutrition delivered at least 7 days prior and up to 14 days postsurgery.[51] A second study from two publications examined short- and long-term outcomes of treatment with omega-3 fatty acid-enriched oral nutrition supplements versus standard oral nutrition supplements for 7 days before and after colorectal cancer surgery.[56, 57] Another study compared EPA-enriched enteral nutrition 5 days prior to surgery versus iso-caloric enteral nutrition through 15 days postsurgery for esophageal cancer.[54] The same group compared the same intervention, also versus iso-caloric enteral nutrition but for 30 days postoperatively.[50] A single study compared amino acids 1 week prior to and for 5 weeks during chemotherapy for gastrointestinal cancer versus standard care.[59] Finally, three studies examined glutamine for immunonutrition. One of these compared parenteral glutamine supplements with enteral nutrition versus enteral nutrition alone for 5 days pre- and postoperatively in colorectal cancer.[53] The second compared

parenteral glutamine solution versus an isonitrogenous control 2 days preoperatively to 5 days postoperatively for pancreatic cancer.[52] The third, outside of the surgical setting, compared glutamine versus placebo for 3 days prior to the initiation of radiation therapy through completion.[60]

The second group of studies examined a combination of supplements for immunonutrition. One study compared immunonutrition-enhanced enteral nutrition with added L-arginine, omega-3 fatty acids, and nucleotides versus standard enteral nutrition, both delivered 2 days preoperatively through 7 days postoperatively for gynecologic cancer.[46] A second study compared immune-enhancing enteral nutrition (with added arginine, nucleotides, and fatty acids) delivered 5 days pre- and 7 days postsurgery versus an iso-caloric nutrition supplement for advanced head and neck cancer.[48] A third study compared immunomodulating nutrition (Oral Impact®) versus Resource 2.0 fiber in patients with gastrointestinal cancer before and after surgery.[61]

The remaining studies evaluated a variety of other supplement combinations. One compared nutrition counseling only versus nutrition counseling with oral whey protein supplementation for 3 months in malnourished advanced cancer patients.[47] Another, a four-arm study, compared omega-3 fatty acid and vitamin D in combination or alone versus a placebo in individuals eligible for chemotherapy for colorectal cancer for 8 weeks.[49] A third study investigated perioperative oral protein supplementation rich in arginine and omega-6 versus placebo in patients with gastrointestinal cancer undergoing surgery.[55] Studies were not U.S.-based, and were primarily conducted in Europe and Asia. Overall, studies differed widely in type of dietary supplements administered, route of administration, and control populations.

Route or Timing of Nutrition Interventions

Eligible Studies

Table 6.3 summarizes the characteristics of the literature set. We identified nine unique studies that examined the route or timing of nutrition interventions initiated prior to and continued after cancer treatment.[62-70] Many studies enrolled 100 or more individuals. The primary outcomes of these studies varied considerably, with some seeking to assess the impact of the nutrition intervention on clinical laboratory outcomes such as components of a metabolic panel[64, 69] and nutrition indicators,[70] as well as body weight or composition changes.[67, 69, 71] Others had primary endpoints that assessed reductions in postoperative infections[62, 65, 66, 68] or length of hospital stay.[62, 66] Studies rarely indicated that the intervention was delivered by a dietitian/nutritionist (n=1), and almost all populations were treated with surgery alone. Appendix D provides detailed evidence tables.

Table 6.3. Basic characteristics of studies of nutrition interventions prior to and including initiating cancer treatment: route or timing of nutrition interventions

Characteristics	Information
Total Included Studies	9 Studies
Study Sample Size	3 76-100 6 >100
Cancer Type	2 Head & neck 6 Gastrointestinal 1 Multiple cancers
Intervention Delivery Setting	5 Inpatient 3 Multiple settings 1 Not reported

Characteristics	Information
Dominant Cancer Treatment Type of Participants	7 Surgery alone 2 Multiple therapies
Limited to Malnourished Patients	3 Yes 5 No 1 Not reported
Malnourishment Screening Tool Used	3 Other tool/metric 1 Multiple tools/metrics 5 Not reported
Provider Prescribing or Delivering the Intervention	1 Dietitian/nutritionist 1 Physician 7 Not reported
Route of Administration	3 Oral 3 Enteral 3 Other
Geographic Region of Intervention	3 Europe 4 Asia 2 Other
% of Participants with Stage IV Disease	2 25-50% 7 Not reported
% Female Participants	4 0-25% 4 26-50% 1 51-75%
Mean Age of Participants	7 50-64 1 ≥65 1 Not reported
Outcomes Evaluated	4 Body weight or composition changes 2 Changes in nutrition status 6 Adverse events 1 Readmissions or emergency room visits 1 Survival 5 Length of stay

Description of Interventions

Two studies enrolled individuals with head and neck cancer. One study compared enteral nutrition initiated immediately after placement of a prophylactic gastrostomy tube and continued for the duration of treatment versus standard care, which included initiation of enteral nutrition when indicated (e.g., oral intake <60% of estimated energy requirements).[71] A second study conducted a three-armed trial in head and neck cancer and compared 1) perioperative whole oral immunonutrition 7 days preoperatively through 7 to15 days postoperatively, 2) perioperative use of whole oral nutrition without immunonutrients, and 3) preoperative whole oral immunonutrition with a standard diet 4 days postoperatively.[65 67, 68] Six studies examined the timing of nutrition support in individuals with gastrointestinal cancer. One study compared preoperative enteral nutrition administered 1 week prior to gastric cancer surgery and continued 2 days postoperatively versus initiating enteral nutrition 2 days postoperatively.[64] A second study conducted a three-arm trial in gastrointestinal cancer patients comparing the use of either 1) an oral nutrition support five days prior to surgery coupled with intravenous glucose postsurgery, 2) the same preoperative treatment coupled with continued use of same nutrition support postoperatively until oral food resumed, or 3) no preoperative treatment coupled with intravenous glucose postsurgery.[66] Another study compared, in a three-arm trial, preoperative and postoperative whole immunonutrition versus preoperative only, and no use, in individuals undergoing gastrointestinal surgery.[62] A fourth study compared enteral versus parenteral nutrition 3 days prior to the start of chemotherapy through 7 days post completion of

chemotherapy in individuals with esophageal cancer.[67] Another study was a four-arm study examining combinations of whole immunonutrition 7 days pre- and postoperatively versus standard nutrition in individuals with esophageal cancer.[68] Finally, one study conducted in patients with rectal cancer randomized individuals to enteral nutrition support 7 days preoperatively and a fiber-enriched nutrition support for 5 days postoperatively versus parenteral infusion of amino acids and glucose solutions, with similar energy consumption between groups.[70]

One three-arm study included patients undergoing elective surgery for breast and colorectal cancers and compared consumption of a milk-based oral nutrition supplement preoperatively and ending supplementation at either discharge or 90 days post-discharge.[69] These non-U.S. studies took place primarily in Europe and Asia. Overall, studies varied in the type of nutrition administered, populations studied, timing and route of administration, and comparisons.

Nutrition Support Including Oral Nutrition Supplements

Eligible Studies

Table 6.4 summarizes the characteristics of the literature set. We identified 13 unique studies across 16 publications examining nutrition support interventions initiated prior to and continued after the start of cancer treatment.[72-87] Most studies enrolled more than 100 individuals. The primary focus of these studies varied considerably, including changes in postoperative complications,[78, 83-85] length of hospital stay,[80, 87] hospital-free days,[82] clinical laboratory markers of nutrition status,[73] changes in inflammatory mediators,[74] body weight or composition changes,[75] insulin resistance,[79] and decreased morbidity and mortality.[72, 80, 81, 86] Most studies were in gastrointestinal patients (n=10). Studies rarely indicated that the intervention was delivered by a dietitian/nutritionist (n=2) and most populations were treated with surgery alone (n=12). Appendix D provides detailed evidence tables.

Table 6.4. Basic characteristics of studies of nutrition interventions prior to and including initiating cancer treatment: nutrition support including oral nutrition supplements

Characteristics	Information
Total Included Studies	13 Studies
Study Sample Size	1 50-75 2 76-100 10 >100
Cancer Type	1 Head & Neck 10 Gastrointestinal 2 Other cancer types*
Intervention Delivery Setting	9 Inpatient 2 Multiple settings 2 Not reported
Dominant Cancer Treatment Type of Participants	12 Surgery alone 1 Chemotherapy alone
Limited to Malnourished Patients	4 Yes 9 No
Malnourishment Screening Tool Used	2 Nutrition Risk Screening NRS-2002 4 Other tools/metrics 7 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 11 Not reported

Characteristics	Information
Route of Administration	8 Oral 1 Enteral 3 Parenteral 1 Not reported
Geographic Region of Intervention	4 Europe 8 Asia 1 North America
% of Participants with Stage IV Disease	5 <10% 1 >50% 7 Not reported
% Female Participants	3 0-25% 9 26-50% 1 51-75%
Mean Age of Participants	4 50-64 7 ≥65 2 Not reported
Outcomes Evaluated†	4 Body weight or composition changes 12 Adverse events 3 Readmissions or emergency room visits 6 Survival 9 Length of stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Ten studies examined nutrition support in gastrointestinal cancer. One study examined use of an oral nutrition supplement for 2 weeks before gastrectomy and for 4 weeks postoperatively versus unspecified standard care.[78] Another study compared whole immunonutrition for 7 days preoperatively to 5 days postoperatively versus dietary advice alone in colorectal surgery patients.[80] A third study compared oral immunonutrition with an EPA-enriched supplement for 7 days prior to surgery through 21 days after surgery for gastric cancer versus a standard diet.[75, 76] Another three-arm trial among gastric cancer patients randomized individuals to 1) multi-oil fat emulsion 7 days preoperatively and intralipid nutrition 2 to 7 days postoperatively, 2) intralipid nutrition 7 days preoperatively and 2 to 7 days postoperatively, or 3) intralipid nutrition 2 to 7 days postoperatively.[73] A fourth study of individuals with liver cancer compared whole enteral nutrition 3 days preoperatively to 7 days postoperatively versus regular food intake with a targeted energy requirement.[87] A single study compared either parenteral or enteral nutrition delivered 7 days prior to 7 days postoperatively versus standard oral diet preoperatively and parenteral nutrition postoperatively in gastric and colorectal cancer patients.[86] One four-arm study compared a preoperative carbohydrate drink versus placebo and a polymeric formula supplement versus placebo postoperatively for colorectal cancer.[79] Another study investigated pre- and postoperative early oral feeding versus conventional fasting in elderly patients with hepatocellular carcinoma.[74] One study compared peripheral parenteral nutrition in the day before surgery and 3 days after surgery versus conventional fluid therapy in colorectal patients.[83, 84] Finally, a single study compared total parenteral nutrition 10 days preoperatively to 9 days postoperatively in gastrointestinal cancer patients versus a standard preoperative oral diet with postoperative hypocaloric parenteral nutrition.[72]

Three studies examined nutrition support outside of gastrointestinal cancer. One evaluated patients with resectable bladder cancer, comparing an omega-3 fatty acid-enriched oral nutrition supplement versus a multivitamin, with both administered 4 weeks prior through 4 weeks

postsurgery.[82] Another compared amino acid-enriched oral nutrition support 1 week prior to the start of chemoembolization for up to 1 year versus usual diet among individuals with hepatocellular carcinoma.[81] A final study investigated an immune-enhancing diet versus a hospital-prepared blenderized diet 7 days before the operation and 14 days after in head and neck cancer patients. [85] One study was U.S.-based[82] while a majority of the remaining studies were based in Asia. Although all studies examined the use of nutrition support, studies varied in the type and duration of nutrition support, cancer type, and control groups.

Multi-Component Interventions

Eligible Studies

Table 6.5 summarizes the characteristics of the literature set. Only one study examined the use of multi-component interventions initiated prior to and continued after the start of cancer treatment.[88] Appendix D provides detailed evidence tables.

Table 6.5. Basic characteristics of studies of nutrition interventions prior to and including initiating cancer treatment: multi-component interventions

Characteristics	Information
Total Included Studies	1 Study
Study Sample Size	1 >100
Cancer Type	1 Multiple cancers
Intervention Delivery Setting	1 Outpatient
Dominant Cancer Treatment Type of Participants	1 Chemotherapy alone
Limited to Malnourished Patients	1 Yes
Malnourishment Screening Tool Used	1 Not reported
Provider Prescribing or Delivering the Intervention	1 Dietitian/nutritionist
Route of Administration	1 Oral
Geographic Region of Intervention	1 Europe
% of Participants with Stage IV Disease	1 Not reported
% Female Participants	1 26-50%
Mean Age of Participants	1 ≥65
Outcomes Evaluated*	1 Survival

*Studies may evaluate multiple outcomes.

Description of Interventions

Only one study examined a multi-component intervention to improve nutrition. This large four-arm study enrolled individuals willing to undergo palliative chemotherapy for gastrointestinal cancer, lung cancer, or mesothelioma, and randomized participants to 1) no dietary advice, 2) dietary advice to increase food intake to a level needed to achieve body weight gain, 3) daily nutrition support supplements with daily multivitamins, and 4) dietary advice with nutrition support supplements, each for 6 weeks.[88]

Risk of Bias and Outcome Assessment

Table 6.6 summarizes risk of bias. Appendix D provides risk of bias assessments and outcome details.

Table 6.6. Risk of bias assessment for nutrition interventions prior to and including initiating cancer treatment

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types*
Nutrition Counseling	-	-	-	-
Dietary Supplements	-	4 Medium 6 High (N=10)	-	-
Special Diets	-	-	-	-
Route or Timing of Nutrition Interventions	-	-	-	-
Nutrition Support Including Oral Nutrition Supplements	-	2 Low 4 Medium 4 High (N=10)	-	-
Multi-component Interventions	-	-	-	-

Abbreviations: - = risk of bias not performed.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Outcomes for Dietary Supplements

Four medium-risk-of-bias studies across five publications were conducted in the surgical inpatient setting for gastrointestinal cancer patients.[52, 55-58] Study sample sizes ranged from 60 to 195 patients. Body weight changes, adverse events, readmissions, survival, and length of hospital stay were reported by one to four studies for each outcome, but the studies were distributed across interventions that could not be aggregated. All interventions reported no difference in measured outcome except for mid-arm circumference in a study of glutamine supplementation.[52]

Outcomes for Nutrition Support Including Oral Nutrition Supplements

Two low- and four medium-risk-of-bias studies across seven publications examined surgical inpatients for gastrointestinal cancer.[72-74, 79, 80, 83, 84] Study sample sizes ranged from 120 to 317. Length of hospital stay, adverse events, readmission and emergency room visits, and survival were reported in one to six of the studies, but these studies were distributed across interventions that could not be aggregated. Reported results were mixed, with some studies reporting a benefit, and some reporting no difference in improving development of adverse events, length of hospital stay, readmission and emergency room visits, and survival.

Variation in the Effects of Nutrition Interventions on Preventing Negative Outcomes

While studies enrolled individuals from multiple cancer types, treatments, and stages (KQ 1&2a), across the lifespan (KQ 1&2b), with varying degrees of muscle wasting (KQ 1&2c) and in those with a range of comorbid conditions (KQ 1&2d), no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Chapter 7. Nutrition Interventions After Cancer Treatment Began

Key Points

- Studies of nutrition interventions after cancer treatment began examined use of nutrition counseling, dietary supplements, special diets, route or timing of nutrition interventions, nutrition support, and multi-component interventions.
- Studies were predominately conducted among gastrointestinal and head and neck cancer populations, both in inpatient surgical and outpatient settings.
- Of studies assessed for risk of bias, 31 percent (n=8/26) of dietary supplement studies, 54 percent (n=13/24) of nutrition support studies, and 59 percent (n=16/27) of studies evaluating the route or timing of nutrition interventions were high risk of bias (poor quality), with only 10 percent (n=8/77) assessed as low risk of bias.
- Among four low- and 14 medium-risk-of-bias studies in dietary supplements, results were mixed, with most studies reporting no benefit of added dietary supplements on body weight, adverse events, length of hospital stay, or survival. Two low-risk-of-bias studies reported fewer adverse events and decreased length of hospital stay with soybean and fish oil. One medium-risk-of-bias study of glutamine reported improved body weight, reduction in adverse events, and improved treatment tolerance, while another medium-risk-of-bias study reported fewer adverse events branched-chain amino acid (BCAA)-enriched total parenteral nutrition (TPN). One medium-risk-of-bias study found improvement in postoperative complications with enteral and parenteral nutrition supplemented with omega-3 fatty acids. Three studies reported reduced length of hospital stay across diverse supplements.
- Among one low- and 10 medium-risk-of-bias studies that examined route and timing of nutrition interventions, results were mixed. The majority reported no difference for body weight, adverse events, readmissions, or death, but half reported reduced length of hospital stay. One low-risk-of-bias study reported that postoperative enteral nutrition reduced adverse events.
- Among three low- and eight medium-risk-of-bias studies that examined nutrition support (including oral nutrition), results were mixed for body weight, nutrition status, and adverse events. Two low- and three medium-risk-of-bias studies reported improved body weight or composition with postoperative nutrition support. Four of ten studies reported improvements in adverse events, and three reported improvements in length of hospital stay across diverse enteral and oral nutrition support interventions.
- Studies showed high heterogeneity across study populations, interventions, and outcomes, making meta-analysis infeasible.

Overview

This chapter includes studies that addressed Key Question (KQ) 2. Such studies examined nutrition interventions delivered simultaneously (at least in part) with cancer therapy (e.g., systemic therapy, radiation, surgery), regardless of treatment intent (e.g., curative vs. palliative). In contrast, some interventions were delivered prior to the initiation of cancer treatment and

continued after cancer treatment began (addressing KQs 1 and 2), and we present these separately in Chapter 6. For each intervention type, in order to briefly discuss what has been examined, we present results in two general sections: Eligible Studies and Description of Interventions. We assessed risk of bias for intervention/cancer types with a higher volume of studies. This allowed us to identify the greatest amount of lower risk of bias evidence concentrated according to specific nutrition interventions by cancer type. The number of studies by intervention type and cancer type for which we assessed risk of bias are bolded in Table 7.1. For interventions with low- to medium-risk-of-bias studies, we note the reported outcome directionality at the end of the chapter. Detailed information on all eligible studies can be found in Appendix E.

For KQ2, we identified 141 studies across 150 publications that examined nutrition interventions after cancer treatment began. Studies examined nutrition counseling (n=15), dietary supplements (n=34), special diets (n=8), route or timing of nutrition interventions (n=31), nutrition support including oral nutrition supplements (n=43), and multi-component interventions (n=10). Table 7.1 summarizes the characteristics of the KQ2 literature set.

Table 7.1. Studies examining use of nutrition interventions after treatment began, stratified by intervention type and cancer type

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Type†	Total
Nutrition Counseling	3	4	6	2	15
Dietary Supplements	**10***	**16***	3	5	34
Special Diets	0	1	2	5	8
Route or Timing of Nutrition Interventions	4	**24***	1	2	31
Nutrition Support Including Oral Nutrition Supplements	4	**27***	4	8	43
Multi-Component Interventions	2	2	2	4	10
Total	-	-	-	-	141

Abbreviations: - = not applicable

*Indicates risk of bias was performed.

†Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Nutrition Counseling

Eligible Studies

Table 7.2 summarizes the characteristics of the literature set. We identified 15 unique studies that examined nutrition counseling during cancer treatment.[89-103] Four studies enrolled individuals with gastrointestinal cancer, three enrolled those with head and neck cancers, six enrolled people from multiple cancer types, and two addressed other cancer types. Over half of the studies enrolled more than 100 participants. Ten studies reported that the intervention was administered by a dietitian/nutritionist, while four used multiple or other types of providers. Three studies did not report the provider delivering the intervention. While studies varied in their primary intent, almost all assessed the impact of the intervention on body weight or composition, and more than half assessed changes in nutrition status. The primary outcome of these studies, when reported, varied and included mortality,[89] nutrition status,[90, 93-95, 103] symptoms,[91] and body composition.[102] Appendix E provides detailed evidence tables.

Table 7.2. Basic characteristics of studies of nutrition interventions after treatment began: nutrition counseling

Characteristics	Information
Total Included Studies	15 Studies
Study Sample Size	3 50-75 4 76-100 8 >100
Cancer Type	4 Gastrointestinal 3 Head and neck 6 Multiple 2 Other cancer types*
Intervention Delivery Setting	3 Inpatient 11 Outpatient 1 Not reported
Dominant Cancer Treatment Type of Participants	3 Chemotherapy alone 6 Radiation alone 5 Multiple therapies 1 Not reported
Limited to Malnourished Patients	3 Yes 12 No
Malnourishment Screening Tool Used	1 MNA-SF 7 Other tool/metric 4 Multiple tools 3 Not reported
Provider Prescribing or Delivering the Intervention	10 Dietitian/nutritionist 1 Nurse 2 Multiple 1 Other 1 Not reported
Route of Administration	Not applicable
Geographic Region of Intervention	7 Europe 4 Asia 3 Other 1 Not reported
% of Participants with Stage IV Disease	3 0-25% 2 26-50% 2 51-75% 1 76-100% 7 Not reported
% Female Participants	4 0-25% 9 26-50% 2 Not reported
Mean Age of Participants	7 50-64 7 ≥65 1 Not reported
Outcomes Evaluated†	12 Body weight or composition changes 9 Changes in nutrition status 6 Adverse events 1 Readmission or emergency room visits 6 Survival 1 Length of stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Four studies evaluated standardized intensive nutrition counseling. One compared intensive nutrition counseling versus on-demand counseling in head and neck cancer patients undergoing chemoradiotherapy, with the groups differing in the number of nutrition consultations during treatment.[95] One study compared intensive nutrition counseling following the standard nutrition protocol of the Academy of Nutrition and Dietetics (AND) versus patients who received one routine educational session across multiple cancer types during and after radiotherapy.[101] One study also compared intensive nutrition counseling following a predetermined standard nutrition protocol (medical nutrition therapy protocol of AND) versus usual care in patients with various cancers of the gastrointestinal tract and head and neck who were undergoing radiotherapy.[92] Finally, one study examined individual sessions with a dietitian (aimed at increasing soluble fiber and decreasing lactose in the diet) through 8 weeks of radiation therapy, versus standard care, in individuals with prostate cancer.[91]

A second group of studies evaluated individualized nutrition counseling. One included patients with head and neck cancer undergoing chemoradiotherapy.[93] A second included patients with colorectal cancer undergoing radiotherapy,[98] and the third included colorectal cancer patients undergoing chemotherapy.[102] Another study compared guideline-based nutrition education counseling based on the patient's Patient-Generated Subjective Global Assessment score versus no nutrition education in patients undergoing radiation therapy across multiple cancer types.[103]

A third group of studies examined face-to-face interviewing. One multicenter trial compared counseling based on face-to-face interviewing and dietary advice cards in patients across multiple cancer types undergoing chemotherapy versus usual care.[89] A second study also compared dietary advice consisting of face-to-face interviews conducted during chemotherapy in patients across multiple cancer types.[99]

The remaining studies were more diverse. One compared a standardized dietary advice approach for foods to avoid and consume in patients with prostate cancer undergoing radiotherapy.[96] Another study included patients across multiple cancer types who were given nutrition consulting and meal planning during the first week postdischarge.[100] A whole-course nutrition management model was used in one study for patients with gastrointestinal cancer undergoing chemoradiotherapy versus a general nutrition method.[97] One study compared medical nutrition therapy involving individualized dietary planning, nutrition education, and pharmacotherapy versus general nutrition advice in patients with gastrointestinal cancer undergoing chemoradiation.[94] A final study evaluated the Eating as Treatment (EAT) program, which is based on motivational interviewing and cognitive behavioral therapy. Participants in this study were undergoing radiation for head and neck cancer.[90] Most of these non-U.S. studies were conducted in Europe and Asia.

Dietary Supplements

Eligible Studies

Table 7.3 summarizes the characteristics of the literature set. We identified 34 unique studies across 35 publications that examined dietary supplements administered after the start of cancer treatment.[104-138] Half of the studies enrolled between 50 and 75 participants. Studies varied in their intent, but many focused on improving biomarkers of nutrition status[107, 109-112, 122, 127, 128, 135] or immune function[118, 131, 132, 135] rather than clinical outcomes. Some studies, however, did focus

on clinical endpoints such as changes in side effects, adverse events, length of hospital stay, and survival.[106, 117, 119, 125, 135] Appendix E provides detailed evidence tables.

Table 7.3. Basic characteristics of studies of nutrition interventions after treatment began: dietary supplements

Characteristics	Information
Total Included Studies	34 Studies
Study Sample Size	17 50-75 7 76-100 10 ≥100
Cancer Type	10 Head and neck 16 Gastrointestinal 3 Multiple cancers 5 Other cancer types*
Intervention Delivery Setting	17 Inpatient 9 Outpatient 1 Other 7 Not reported
Dominant Cancer Treatment Type of Participants	20 Surgery alone 5 Chemotherapy alone 1 Radiation alone 7 Multiple therapies 1 Not reported
Limited to Malnourished Patients	5 Yes 29 No
Malnourishment Screening Tool Used	4 Nutrition Risk Screening NRS-2002 1 Multiple tools/metrics 6 Other tool/metric 23 Not reported
Provider Prescribing or Delivering the Intervention	1 Dietitian/nutritionist 2 Nurse 3 Physician 1 Other provider 4 Multiple providers 23 Not reported
Route of Administration	11 Oral 13 Enteral 9 Parenteral 1 Other
Geographic Region of Intervention	14 Europe 19 Asia 1 Other
% of Participants with Stage IV Disease	6 ≤10% 5 11-25% 1 26-50% 6 51-75% 3 76-100% 13 Not reported
% Female Participants	14 0-25% 15 26-50% 1 51-75% 3 76-100% 1 Not reported
Mean Age of Participants	2 <50 21 50-64 7 ≥65 4 Not reported

Characteristics	Information
Outcomes Evaluated†	20 Body weight or composition changes 5 Changes in nutrition status 26 Adverse events 3 Readmissions or emergency room visits 12 Survival 18 Length of stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Overall, studies fell into two categories: single and multi-component supplements.

Single Supplements

Several studies examined the effects of a single supplement for immunonutrition (eicosapentaoenoic acid (EPA), omega-3 fatty acids, or glutamine or arginine-enriched nutrition), but interventions varied by population and ranged widely for intervention durations around the time of cancer surgery. In the surgically treated populations, six studies examined arginine-enhanced oral or enteral nutrition support, but these studies varied in the cancers studied, length of follow up, and comparators (e.g., standard nutrition support, different concentrations of the dietary supplement). One study compared an arginine-enhanced nutrition support supplement compared versus a standard formula after head and neck cancer surgery approximately 4 days postoperatively,[107] while another two studies examined higher doses[111] or longer durations.[109] Another two studies compared higher versus lower ratios of arginine-enhanced enteral feeding, but varied in duration (e.g., 10 versus 15 days postsurgery) and in supplement concentration.[112, 113]

A second group of studies examined omega-3 fatty acids, fish oil, or amino acids in surgically treated patients. One study compared intravenous soybean oil plus fish oil emulsion versus soybean oil alone for 7 days postsurgery for gastrointestinal cancer.[118] Two studies compared omega-3-fatty-acid-enriched TPN 5 days[134] and 7 days[138] postsurgery in different cancers, while a third compared omega-3-fatty-acid-enhanced oral nutrition support versus arginine-enhanced formula for 12 weeks postsurgery in head and neck cancer.[113] Two additional studies compared amino or fatty acid-enriched TPN versus standard TPN for approximately 1 week after gastrointestinal cancer surgery, but with distinct primary outcomes.[127, 137] One study compared enteral nutrition combined with parenteral nutrition enriched with omega-3 polyunsaturated fatty acids versus enteral nutrition combined with standard parenteral nutrition among gastric cancer patients after elective radical gastrectomy. [135] Another study examined the use of an oral omega-3 fatty acid supplement for 12 weeks among lung cancer patients undergoing chemotherapy.[104] Another compared olive oil-based lipid emulsion versus medium/long chain triglycerides for 7 days postsurgery among individuals with esophageal cancer.[132]

In surgical patients, a final set of studies examined the use of glutamine. One study compared glutamine-enhanced total parenteral nutrition versus standard TPN for 7 days postsurgery for gastrointestinal cancer,[122] while the other three-arm trial examined glutamine and omega-3 fatty acids for 1 week in surgically treated gastric cancer patients versus standard TPN.[119]

In individuals undergoing chemotherapy or radiation, five studies examined omega-3 fatty acids, fish oil, or amino acids in different forms. One study compared an amino acid-enriched

snack versus no snack for 2 weeks during chemoembolization for hepatocellular carcinoma,[128] while another examined the use of orally administered amino acid jelly, Inner Power®, for 21 days among breast cancer patients undergoing chemotherapy.[117] Three additional studies examined omega-3 fatty acid supplements in varying doses, but the interventions ranged from 12 days[124] to 12 weeks[110] in head and neck cancer, and 8 weeks in colorectal cancer.[116]

Three studies examined glutamine among individuals undergoing chemotherapy or radiation. One compared glutamine injection plus TPN versus TPN alone for individuals with advanced gastric cancer undergoing chemotherapy,[131] while another examined glutamine for 7 weeks in head and neck cancer.[125] The remaining study compared glutamine-enhanced TPN versus standard TPN for 6 days after allogeneic stem cell transplantation in individuals with leukemia.[106]

Of the two remaining studies, one five-arm study evaluated the combinations of EPA, l-cartinine, thalidomide, and medroxyprogesterone acetate/megestrol acetate (MA) for up to 4 months in individuals with cancer cachexia across different tumor types;[129] and the other compared twice daily Echium oil versus placebo for 7 weeks during chemoradiation for head and neck cancer.[126]

Multi-Component Supplements

Five studies examined multiple supplements postoperatively to improve nutrition and clinical outcomes. One compared EPA and gamma-linolenic acid (GLA) enriched enteral nutrition, Oxepa®, versus standard enteral nutrition for up to 21 days postsurgery among individuals with esophageal cancer.[123] Another evaluated medium chain triglycerides and protein-enriched enteral nutrition, Nutrison® MCT, versus standard enteral nutrition for 5 days after surgery for gastrointestinal cancer.[133] A third compared an arginine, omega-3 fatty acids, and ribonucleic acid (RNA) enriched whole enteral nutrition versus standard whole enteral nutrition for up to 7 days postoperatively in individuals undergoing surgery for gastric cancer.[114] Similarly, a single study compared an arginine, glutamine, and cysteine-enhanced whole enteral nutrition, Stresson-Nutricia®, versus standard whole enteral nutrition for 10 to 15 days postoperatively in gastrointestinal cancer patients.[120] Finally, one study examined immunonutrition, Cubitan® Nutricia, twice daily for 5 days versus standard nutrition for 5 days after pancreatic cancer surgery.[130]

Three studies examined the use of multiple supplements during chemotherapy or radiation therapy. One study compared arginine, glutamine, and fish oil supplementation twice a day during radiation therapy for head and neck, esophageal, and cervical cancer versus a regular diet for approximately 6 weeks.[105] A second study evaluated EPA and docosahexaenoic acid (DHA) enhanced nutrition support versus standard nutrition support via a percutaneous endoscopic gastrostomy (PEG) tube among head and neck cancer patients receiving chemoradiation for a maximum of 14 weeks.[115] A third study compared omega-3 fatty acid, glutamine, probiotic, and vitamin-enriched oral nutrition support versus standard oral nutrition support for 3 months in cachexic head and neck cancer patients undergoing chemoradiation.[136]

Studies in dietary supplements were predominately conducted within Europe and Asia. Overall, studies varied in the type of supplements administered, route of administration, and comparison group during the delivery of cancer treatment.

Special Diets

Eligible Studies

Table 7.4 summarizes the characteristics of the literature set. We identified eight unique studies across nine publications that examined special diets after the initiation of cancer treatment.[139-147] Most studies had sample sizes greater than 100. The primary focus of the studies varied significantly and included changes in symptoms,[140] quality of life,[144] adverse events,[139, 145] treatment toxicity,[147] survival,[146] and multiple primary outcomes.[142, 143] Most studies were in cancers other than gastrointestinal. Appendix E provides detailed evidence tables.

Table 7.4. Basic characteristics of studies of nutrition interventions after treatment began: special diets

Characteristics	Information
Total Included Studies	8 Studies
Study Sample Size	1 50-75 3 76-100 4 >100
Cancer Type	1 Gastrointestinal 2 Multiple cancers 5 Other cancer types*
Intervention Delivery Setting	2 Inpatient 5 Outpatient 1 Not reported
Dominant Cancer Treatment Type of Participants	1 Surgery alone 4 Chemotherapy alone 2 Radiation alone 1 Multiple therapies
Limited to Malnourished Patients	8 No
Malnourishment Screening Tool Used	8 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 1 Physician 5 Not reported
Route of Administration	7 Oral 1 Other
Geographic Region of Intervention	3 North America 3 Europe 1 Asia 1 Other
% of Participants with Stage IV Disease	1 26-50% 1 76-100% 6 Not reported
% Female Participants	1 26-50% 2 51-75% 3 76-100% 2 Not reported
Mean Age of Participants	4 50-64 2 ≥65 2 Not reported
Outcomes Evaluated†	4 Body weight or composition changes 3 Adverse events 2 Survival 1 Length of stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Two studies evaluated the use of specific drinks. One compared the use of a glass of wine before eating along with additional oral nutrition support, such as Boost® or Ensure®, for 3 to 4 weeks during treatment for advanced cancer versus oral nutrition support supplementation alone.[141] Another compared grape juice versus placebo prior to meals for one week following each of four cycles of chemotherapy.[140]

Another three studies examined fasting or calorie restriction. One study compared a ketogenic diet for 3 months versus standard diet in women with metastatic breast cancer undergoing chemotherapy,[142, 143] while the second compared a fasting mimicking diet versus regular diet at the initiation of chemotherapy for breast cancer.[144] The third study compared a calorie-restricted ketogenic diet and fasting versus a calorie-unrestricted diet for recurrent gliomas during radiation therapy.[146]

The remaining studies examined modified diets by consistency or contents. One study examined early initiation of a solid versus liquid diet after surgery for gastrointestinal cancer.[145] A second study compared a diet containing no raw fruits or vegetables (cooked diet) versus a diet containing fresh fruits and vegetables for individuals undergoing induction therapy for acute myeloid leukemia.[139] Finally, one study compared diets that were either low-fat, modified-fat, or normal fat diet in individuals undergoing radiation therapy for pelvic malignancies.[147] Studies were predominately conducted in North America and Europe. Overall, studies evaluating special diets varied in approach, populations, cancer treatments, and comparison groups.

Route or Timing of Nutrition Interventions

Eligible Studies

Table 7.5 summarizes the characteristics of the literature set. We identified 31 unique studies that examined the route or timing of nutrition interventions delivered, at least in part, during cancer treatment.[148-178] Samples sizes were large, with most studies enrolling over 100 individuals. Most studies examined adverse events[62, 137, 148, 149, 154, 157, 160-162, 165-169, 171-173, 175, 176, 179] and length of hospital stay.[62, 149, 159, 160, 162, 165-167, 169, 171-173, 175, 176, 178, 179] Twenty-four studies enrolled individuals with gastrointestinal cancers and four enrolled those with head and neck cancers. In seven studies, the intervention was delivered by a physician, one by a dietitian/nutritionist, and three by multiple providers. The primary cancer treatment was surgery alone. Appendix E provides detailed evidence tables.

Table 7.5. Basic characteristics of studies of nutrition interventions after treatment began: route or timing of nutrition interventions

Characteristics	Information
Total Included Studies	31 Studies
Study Sample Size	4 50-75 8 76-100 19 >100
Cancer Type	24 Gastrointestinal 4 Head and neck 1 Multiple cancers 2 Other cancer types*
Intervention Delivery Setting	27 Inpatient 1 Multiple settings 3 Not reported

Characteristics	Information
Dominant Cancer Treatment Type of Participants	25 Surgery alone 1 Chemotherapy alone 4 Multiple therapies 1 Not reported
Limited to Malnourished Patients	3 Yes 27 No 1 Not reported
Malnourishment Screening Tool Used	3 Nutrition Risk Screening NRS-2002 1 Malnutrition Universal Screening Tool (MUST) 1 MNA 6 Other tool/metric 2 Multiple tools 19 Not reported
Provider Prescribing or Delivering the Intervention	1 Dietitian/nutritionist 7 Physician 3 Multiple 20 Not reported
Route of Administration	12 Oral 2 Parenteral 12 Enteral 5 Other 1 Not reported
Geographic Region of Intervention	20 Asia 9 Europe 1 North America 1 Other
% of Participants with Stage IV Disease	8 <10% 1 10-24% 2 25-49% 2 50-74% 1 75-100% 17 Not reported
% Female Participants	6 0-24% 20 25-49% 1 50-74% 2 75-100% 2 Not reported
Mean Age of Participants	2 40-49 16 50-64 7 65+ 6 Not reported
Outcomes Evaluated†	12 Body weight or composition changes 6 Changes in nutrition status 28 Adverse events 2 Readmission or emergency room visits 10 Survival 22 Length of stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Sixteen studies compared enteral nutrition versus parenteral nutrition. Of those, 14 compared enteral nutrition versus parenteral nutrition in postoperative individuals; most of the 14 enrolled individuals with gastrointestinal cancer,[62, 155, 158-162, 165, 173, 175-177, 179] with only one study investigating those with laryngeal and pharyngeal cancer.[167] A portion of these studies evaluated more specific populations, including gastric cancer patients with diabetes mellitus,[175] patients

with gastrointestinal cancer who were malnourished,[179] and cholangiocarcinoma patients with malignant obstructive jaundice.[162] Another study compared early enteral nutrition versus early parenteral nutrition in rectal carcinoma patients who had undergone after major rectal surgery and were recovering from neoadjuvant chemoradiation.[149] The final study, which compared enteral versus parenteral nutrition methods, enrolled esophageal cancer patients undergoing neoadjuvant chemotherapy.[157]

Six studies compared oral feeding versus enteral or parenteral methods. Five of these compared early oral feeding versus enteral nutrition. Two of these studies evaluated esophageal cancer patients after minimally invasive esophagectomy and the use of early oral feeding versus a jejunostomy tube[148]and a nasoenteral feeding tube.[171] Two studies compared early oral feeding versus a nasogastric tube; one enrolled postoperative gastric cancer patients[154] and the other enrolled patients who underwent elective colorectal resection.[153] Another study that investigated early oral feeding and enteral nutrition was conducted in patients who underwent total laryngectomy and were randomized to receive early oral nutrition or a tracheosophageal puncture.[169] Finally, one study compared total parenteral nutrition versus an oral diet in breast cancer patients undergoing high-dose chemotherapy and hematopoietic cell transplantation.[166]

Three studies evaluated the effects of different enteral or parenteral methods. One compared a percutaneous endoscopic gastrostomy tube versus a nasogastric tube in head and neck cancer patients undergoing curative treatment including radical surgery with adjuvant radiotherapy, chemoradiotherapy, or concurrent chemo- and radiation therapy.[168] Another examined the use of jejunostomy feeding or nasogastric feeding in patients after a minimally invasive McKeown esophagectomy.[172] A third compared a peripherally inserted central catheter versus a central venous catheter in gastric cancer patients after a radical gastrectomy.[178]

Finally, five studies examined the timing of oral feeding after cancer surgery. One compared early (postoperative day 1) versus delayed (postoperative day 4) oral feeding after gastrectomy,[174] while two others examined early versus delayed feeding but used resolution of ileus to initiate delayed feeding in gastrointestinal[163] and gynecologic cancers.[180] Another study compared early feeding on postoperative day 0 compared versus standard delayed feeding until first stool.[152] The last study compared early (postoperative day 1) versus delayed (postoperative day 7) in colorectal cancer surgery.[170] Studies were predominately conducted in Asia and Europe. Overall, studies varied in terms of duration of intervention, cancer therapy received, comparisons, and primary outcomes.

Nutrition Support Including Oral Nutrition Supplements

Eligible Studies

Table 7.6 summarizes the characteristics of the literature set. We identified 43 unique studies across 49 publications that examined nutrition support interventions during cancer treatment.[181-229] Studies varied in sample size, with just under half enrolling more than 100 participants. The primary focus of these studies varied considerably; including changes in postoperative complications,[199-204, 212, 217] biomarkers of nutrition status,[186, 188, 216, 225] body weight changes,[190, 206, 222] quality of life,[191, 220] and length of hospital stay,[204, 218] among others. Most studies enrolled gastrointestinal patients. Only in some studies was the intervention delivered by a dietitian/nutritionist (n=6), and across studies cancer treatment varied substantially. Appendix E provides detailed evidence tables.

Table 7.6. Basic characteristics of studies of nutrition interventions after treatment began: nutrition support including oral nutrition supplements

Characteristics	Information
Total Included Studies	43 Studies
Study Sample Size	9 50-75 14 76-100 20 >100
Cancer Type	4 Head and neck 27 Gastrointestinal 4 Multiple cancers 8 Other cancer types*
Intervention Delivery Setting	21 Inpatient 14 Outpatient 4 Other 4 Not reported
Dominant Cancer Treatment Type of Participants	20 Surgery alone 6 Chemotherapy alone 3 Radiation alone 14 Multiple therapies
Limited to Malnourished Patients	8 Yes 35 No
Malnourishment Screening Tool Used	8 Nutrition Risk Screening NRS-2002 1 MNA 3 Multiple Tools 9 Other tools/metrics 22 Not reported
Provider Prescribing or Delivering the Intervention	5 Dietitian/nutritionist 4 Physician 11 Multiple providers 23 Not reported
Route of Administration	26 Oral 12 Enteral 4 Parenteral 1 Other
Geographic Region of Intervention	12 Europe 27 Asia 1 North America 3 Other
% of Participants with Stage IV Disease	22 ≤10% 4 11-50% 5 51-75% 12 Not reported
% Female Participants	11 0-25% 24 26-50% 6 51-75% 1 76-100% 1 Not reported
Mean Age of Participants	2 <50 20 50-64 11 ≥65 10 Not reported
Outcomes Evaluated†	26 Body weight or composition changes 14 Changes in nutrition status 32 Adverse events 4 Readmissions or emergency room visits 12 Survival 13 Length of hospital stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Nutrition support was delivered in three general intervention types: oral or enteral nutrition after surgery, oral or enteral nutrition during chemotherapy and/or radiation, and total parenteral nutrition across cancer treatments.

Oral or Enteral Nutrition After Surgery

Twenty-two studies examined oral or enteral nutrition support after cancer surgery, and they varied in the route and contents of nutrition support delivered as well as the timing of the comparisons. Four studies examined immunonutrition after surgery. One compared two different oral nutrition supplements, enhanced with EPA and DHA, MEIN® versus a low osmotic load oligomeric formula, HINE E-GEL®, for 6 days after surgery for esophageal cancer.[212] One compared immunonutrition, Reconvan, enhanced with glutamine, arginine, and omega-3 fatty acids versus standard enteral nutrition for up to 7 days postsurgery for gastrointestinal cancer,[199-201] while another examined a similar formula for 6 days postoperatively.[217] The fourth study compared immunonutrition, Stresson®, versus standard nutrition support or TPN for 7 days postoperatively across multiple cancers.[202, 203] Another study compared early enteral nutrition versus parenteral nutrition in colon carcinoma patients.[211] Among the remaining studies, the nutrition support varied in contents and quantity, including nutrition support supplements such as Elental®,[193, 194] Jevity®,[204] Racol®,[210] Nutren®,[208, 209] and Nutrison Fibre®.[225] Additionally, studies examined standard nutrition support for widely ranging durations, from 3 days,[204] to 2 weeks,[226] to 1,[187, 223] 2,[186, 191, 193, 194] 3,[209, 210, 228, 230] and 6[213] months postsurgery; one assessed administration until oral diet commenced.[183] Comparison populations varied substantially as well; some studies compared interventions with standard of care, which was often described as dietary advice,[208, 209] while others compared to TPN alone.[188] While most interventions were delivered to head and neck and gastrointestinal cancers patients, two enrolled patients with urologic[189] and gynecologic[182] cancers. Finally, one distinct study evaluated use of iEAT®, food disintegrated on the tongue, versus standard care after surgery for gastrointestinal cancer.[218]

Oral or Enteral Nutrition During Chemotherapy and/or Radiation

Eighteen studies examined oral or enteral nutrition support during chemotherapy or radiation, and they varied in the route and contents of nutrition support delivered as well as the timing of comparisons. Three studies examined EPA enriched oral nutrition support, but varied by type of cancer, including pancreatic,[181] lung,[216] and multiple types of advanced cancer;[197] these studies also varied substantially in duration from 5 weeks[181] to 3 months.[197, 216] Another three studies examined hyper-protein-enhanced nutrition support,[190, 229] Immax®, and omega-3 fatty acid-enriched oral nutrition support[185] for diverse populations and durations.

The remaining studies evaluated standard nutrition support. Four examined nutrition support for the duration of radiation in head and neck,[192, 214] colorectal,[215] and lower gynecological and gastrointestinal cancers.[207] Another six examined oral nutrition support during chemotherapy for leukemia,[227] esophageal,[198] gastrointestinal,[219, 229] pancreatic,[205] and head and neck cancer,[63] and these varied in duration due to the standard of care for chemotherapy regimens across cancer types. Additionally, three studies examined nutrition support during combined chemoradiation. One study compared oral nutrition support, Niufutai®, for the duration of chemoradiation versus regular diet in individuals with advanced head and neck cancer.[195] The other two studies examined use of oral nutrition support versus dietary advice in individuals undergoing

chemoradiation.[206, 224] A final study compared early enteral nutrition support with chemotherapy versus only chemotherapy in gastric cancer patients after a radical gastrectomy.[221]

Total Parenteral Nutrition

Four studies examined TPN across cancer and treatment types. One compared oral feeding supplemented by TPN versus oral feeding alone in individuals with advanced cancer cachexia who were undergoing or had recently completed cancer treatment.[184] A second compared TPN, Olimel®, for 4 to 8 days postsurgery versus isotonic fluids in individuals with gastric cancer.[196]A third compared TPN, Nutriflex®, versus standard diet for 5 days postoperatively in individuals undergoing bladder cancer surgery.[220] A final study compared TPN plus enteral nutrition support, Nutrison®, for approximately 7 days postsurgery for esophageal cancer versus enteral nutrition support alone.[222]

Multi-Component Interventions

Eligible Studies

Table 7.7 summarizes the characteristics of the literature set. Ten studies across 11 publications examined multi-component interventions initiated after cancer treatment began.[231-241] The primary focus was to assess laboratory markers of immune and nutrition status,[232, 233, 235, 239, 241] body weight changes,[236-238] and symptoms.[231] Half of the studies enrolled over 100 participants, and interventions were most often delivered or prescribed by a dietitian or nutritionist. Most studies were conducted outside of the United States. Appendix E provides detailed evidence tables.

Table 7.7. Basic characteristics of studies of nutrition interventions after treatment began: multi-component interventions

Characteristics	Information
Total Included Studies	10 Studies
Study Sample Size	3 50-74 2 75-100 5 >100
Cancer Type	2 Head and neck 2 Gastrointestinal 2 Multiple cancers 4 Other cancer types*
Intervention Delivery Setting	5 Outpatient 4 Multiple settings 1 Not reported
Dominant Cancer Treatment Type of Participants	1 Surgery Alone 5 Chemotherapy alone 3 Multiple therapies 1 Not reported
Limited to Malnourished Patients	3 Yes 7 No
Malnourishment Screening Tool Used	3 Nutrition Risk Screening NRS-2002 2 Other tool 5 Not assessed
Provider Prescribing or Delivering the Intervention	6 Dietitian/nutritionist 1 Nurse 2 Multiple 1 Not reported

Characteristics	Information
Route of Administration	5 Oral 4 Other 1 Enteral
Geographic Region of Intervention	4 Asia 4 Europe 1 North America 1 Other
% of Participants with Stage IV Disease	2 ≤10% 2 11-50% 1 51-75% 5 Not reported
% Female Participants	1 0-25% 5 26-50% 1 51-75% 3 76-100%
Mean Age of Participants	3 <50 4 50-64 2 ≥65 1 Not reported
Outcomes Evaluated†	7 Body weight or composition changes 5 Changes in nutrition status 3 Adverse outcomes 1 Readmissions or emergency room visits 3 Survival 2 Length of hospital stay

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Multi-component interventions varied in the interventions administered, cancer type, comparators, and cancer treatments. Three studies examined individualized diet or nutrition plans combined with additional interventions such as education or counseling. One study compared a one-time face-to-face nutrition education session with a trained dietitian along with an individualized diet versus standard care in women undergoing chemotherapy for breast cancer.[231] One study compared an intensive individualized nutrition diet plan and educational advice throughout the course of chemotherapy versus basic nutrition and education advice during hospitalization for gastric cancer.[241] Another study compared nutrition education combined with oral nutrition supplementation (Ensure®) versus nutrition education alone in ovarian cancer patients undergoing chemotherapy.[235] Finally, one study compared an individualized nutrition plan including nutrition counseling and dietary interventions such as oral nutrition support or protein rich snacks for 3 months versus standard care in individuals with cancer.[240]

The remaining studies varied widely in interventions administered. One compared individual recipes developed by patients, caregivers, and clinical specialists along with supplemental enteral or parenteral nutrition to meet energy requirements versus nutrition guidance alone in individuals undergoing chemotherapy for colorectal cancer.[233] One three-arm study examined 1) a calcium rich diet, 2) a calcium rich diet plus exercise, or 3) a calcium rich, low-fat and high-fruit and vegetable diet plus exercise in women with breast cancer undergoing chemotherapy.[232] Another study compared a prophylactic percutaneous endoscopic gastrostomy (PEG) tube for early enteral feeding along with nutrition advice versus standard care in patients undergoing treatment for head and neck cancer.[236, 237] A fourth compared oral, enteral, or TPN nutrition support during hospitalization followed by nutrition education support and provision of oral nutrition support

postdischarge versus standard care among individuals hospitalized for hematopoietic stem cell transplant.[238] Finally, one study examined in-hospital nutrition education and early enteral nutrition support (24 hours after surgery) that continued 6 weeks postoperatively versus regular enteral nutrition support (48 hours after surgery) in individuals treated for laryngeal cancer.[239]

Risk of Bias and Outcome Assessment

Table 7.8 summarizes risk of bias assessments. Appendix E provides risk of bias assessments and outcomes.

Table 7.8. Risk of bias assessment for nutrition interventions after treatment began

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types*
Nutrition Counseling	-	-	-	-
Dietary Supplements	6 Medium 4 High (N=10)	4 Low 8 Medium 4 High (N=16)	-	-
Special Diets	-	-	-	-
Route or Timing of Nutrition Interventions	-	1 Low 10 Medium 13 High (N=24)	-	-
Nutrition Support Including Oral Nutrition Supplements	-	3 Low 8 Medium 16 High (N=27)	-	-
Multi-Component Interventions	-	-	-	-

Abbreviations: - = risk of bias not performed.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Outcomes for Dietary Supplements

Four low- and 14 medium-risk-of-bias studies evaluated use of dietary supplements during cancer treatment.[109-112, 114, 116, 118, 120, 122, 124-128, 132, 133, 135, 138] Studies were one-third head and neck cancers (n=6/18) and two-thirds gastrointestinal cancers (n=12/18). Four of the six head and neck cancer studies were surgical only populations, while nine of the 11 gastrointestinal cancer populations were surgical. Study sample sizes were small to large, from 50 to 229 patients, and12 studies were under 100 patients. All studies of head and neck cancers reported body weight and composition changes but less than one-half (5/12) of the gastrointestinal cancer studies did so. Gastrointestinal cancer studies focused more on length of hospital stay as an outcome (8/12). Additionally, studies examined a wide range of interventions and outcome timing with little overlap, creating concerns about whether grouping or aggregation would be appropriate. Outcomes were mixed, with most studies reporting no benefit of added dietary supplements on body weight, adverse events, length of hospital stay, or survival. Two low-risk-of-bias studies reported benefits with soybean and fish oil for fewer adverse events and decreased length of hospital stay.[118, 138] One medium-risk-of-bias study of glutamine reported improved body weight, reduction in adverse events, reduction in length of hospital stay and

improved treatment tolerance,[125] while another medium-risk-of-bias study reported a benefit of BCAA-enriched TPN for reducing adverse events.[127] Another medium-risk-of-bias study found improvement in postoperative complications with enteral and parenteral nutrition supplemented with omega-3 fatty acids.[135] Three studies reported improvements in length of hospital stay across diverse supplements.[111, 114, 133]

Outcomes for Route or Timing of Nutrition Interventions

One low- and 10 medium-risk-of-bias studies evaluated the route or timing of nutrition interventions during cancer treatment.[148, 150, 151, 153, 158, 162, 171, 172, 174-176] Populations were overwhelmingly surgical inpatients (10 of 11 studies). Sample sizes were midrange, from 60 to 317 patients. The most common outcome categories were body weight (4 studies), adverse events (9 studies), length of hospital stay (8 studies), and death (4 studies). Studies examined a wide range of populations, interventions, and outcome timing, with little overlap, creating concerns about whether grouping or aggregation would be appropriate. Studies reported mixed results, with the majority finding no difference based on route or timing of nutrition interventions for changes in body weight, adverse events, readmissions, or death, while half showed an improvement in length of hospital stay. One low-risk-of-bias study reported that postoperative enteral nutrition reduced adverse events and length of hospital stay.[150]

Outcomes for Nutrition Support (Including Oral Nutrition Supplements)

Three low- and eight medium-risk-of-bias studies evaluated use of nutrition support during cancer treatment.[183, 188, 199-203, 205, 208-210, 222, 223, 225, 228] Studies were overwhelmingly inpatients receiving oral or enteral nutrition after surgery (10 of 11 studies). Study sample sizes were midrange, from 78 to 1003. The most common outcome categories were body body weight/composition changes (5 studies), adverse events (10 studies), and length of hospital stay (6 studies). Studies were distributed across a wide range of populations, interventions, and outcome timing, with little overlap, creating concerns about whether grouping or aggregation would be appropriate. Two low-[208, 228] and three medium-risk-of-bias studies[210, 222, 223] reported improvements in body weight or composition with postoperative nutrition support. Four out of ten studies[183, 188, 205, 225] reported improvements in adverse events and three reported improvements in length of hospital stay[183, 188, 225] across diverse enteral and oral nutrition support interventions.

Variation in the Effects of Nutrition Interventions on Preventing Negative Outcomes

While studies enrolled individuals from multiple cancer types, treatments, and stages (KQ2a), across the lifespan (KQ2b), with varying degrees of muscle wasting (KQ2c) and in those with a range of comorbid conditions (KQ2d), no eligible studies specifically evaluated whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Chapter 8. Effect of Nutrition Interventions on Symptoms

Key Points

- Studies of the effects of nutrition interventions on symptoms included nutrition counseling, use of dietary supplements, special diets, route or timing of nutrition interventions, and nutrition support (including oral nutrition supplements).
- Studies were predominately conducted among gastrointestinal and head neck cancer populations, both in inpatient surgical and outpatient settings.
- Of studies assessed for risk of bias, 40 percent (n=2/5) of dietary supplement studies and 55 percent (n=11/20) of nutrition support studies were high risk of bias (poor quality), with only 20 percent (n=5/20) low risk of bias.
- Among three medium-risk-of-bias studies in dietary supplements, one study of probiotics and omega-3 fatty acids reported improvement in quality of life and the other reported no benefit with perioperative oral protein supplementation. The studies reported mixed outcomes for patient-reported symptoms, with one reporting a benefit and one reporting no difference. One study of probiotics and omega-3 fatty acids reported improvement in quality of life, while another reported no benefit. Two studies reported mixed outcomes for patient-reported symptoms with one reporting a benefit and one no difference. [133 133 133 133 133 43]
- Among Five low- and four medium-risk-of-bias studies of nutrition support, results were mixed. Two studies showed mixed results for functional status, with one finding a benefit and one no difference. Two low-risk-of-bias studies reported improvement in nausea for individuals receiving preoperative oral carbohydrate drinks. A third low-risk-of-bias study reported improvement in treatment tolerance and symptoms after use of oral nutrition supplements and dietary advice.
- Studies showed high heterogeneity across study populations, interventions, and outcomes, making meta-analysis infeasible.

Overview

This chapter includes studies that addressed Key Question (KQ) 3. Such studies examined the effect of nutrition interventions delivered prior to or during cancer treatment on associated cancer and treatment-related symptoms such as fatigue, nausea and vomiting, appetite, physical and functional status, and quality of life. Because studies often examined the impact of nutrition interventions on preventing and treating negative treatment outcomes either prior to (KQ1) or during (KQ2) cancer treatment as well as the impact on improving symptoms (KQ3), many studies in this chapter have also been presented in Chapters 5 - 7.

For each intervention type, in order to briefly discuss what has been examined, we present results in two general sections: Eligible Studies and Description of Interventions. We assessed risk of bias for intervention/cancer types with a higher volume of studies. This allowed us to identify the greatest amount of lower risk of bias evidence concentrated according to specific nutrition interventions by cancer types. The number of studies by intervention type and cancer type for which we assessed risk of bias is indicated in Table 8.1. For interventions with low- to medium-risk-of-bias studies, we note the reported outcome directionality at the end of the

chapter. For all studies, we present a brief discussion of what has been examined. Detailed information on all eligible studies can be found in Appendix F.

For KQ3, we identified 79 studies across 83 publications that examined nutrition interventions after cancer treatment began. Studies examined nutrition counseling (n=12), dietary supplements (n=10), special diets (n=10), route or timing of nutrition interventions (n=8), nutrition support (including oral nutrition supplements) (n=32), and multi-component interventions (n=7). Table 8.1 summarizes the characteristics of the KQ3 literature set.

Table 8.1. Studies examining effect of nutrition interventions on symptoms, stratified by intervention type and cancer type

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types†	Total
Nutrition Counseling	1	4	4	3	12
Dietary Supplements	1	**5***	3	1	10
Special Diets	0	1	2	7	10
Route or Timing of Nutrition Interventions	2	4	1	1	8
Nutrition Support Including Oral Nutrition Supplements	5	**20***	3	4	32
Multi-Component Interventions	2	0	3	2	7
Total	-	-	-	-	**79**

Abbreviations: - = Not applicable.
*Risk of bias was performed.
†Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Nutrition Counseling

Eligible Studies

Table 8.2 summarizes the characteristics of the literature set. We identified 12 unique studies examining nutrition counseling on improving cancer symptoms prior to or during cancer treatment.[90-92, 94, 96-99, 101-103, 242] Four of the studies were in populations with gastrointestinal cancer,[94, 97, 98, 102] while the remaining eight studies were conducted in populations with head and neck cancer, multiple cancer types, or those that fell into the defined 'other cancer types' group. Most studies had study populations greater than 100. Most studies reported that the intervention was administered by a dietitian/nutritionist. While the primary focus of the studies varied, almost all assessed the impact of the intervention on quality of life; about half evaluated symptoms or functional status. Appendix F provides detailed evidence tables.

Table 8.2. Basic characteristics of studies of effect of nutrition interventions on symptoms: nutrition counseling

Characteristics	Information
Total Included Studies	12 Studies
Study Sample Size	5 76-100 7 >100
Cancer Type	4 Gastrointestinal 1 Head and neck 4 Multiple 3 Other cancer types*

Characteristics	Information
Intervention Delivery Setting	2 Inpatient 7 Outpatient 3 Not reported
Dominant Cancer Treatment Type of Participants	3 Chemotherapy alone 6 Radiation alone 3 Multiple therapies
Limited to Malnourished Patients	2 Yes 10 No
Screening Tool Used	6 Other tool 2 Multiple tools 4 Not reported
Provider Prescribing or Delivering the Intervention	8 Dietitian/nutritionist 1 Nurse 1 Multiple 1 Other 1 Not reported
Route of Administration	Not applicable
Geographic Region of Intervention	4 Europe 4 Asia 3 Other 1 Not reported
% of Participants with Stage IV Disease	1 0-25% 1 26-50% 1 51-75% 1 76-100% 8 Not reported
% Female Participants	4 0-25% 7 26-50% 1 76-100%
Mean Age of Participants	6 <65 6 ≥65
KQ3 Outcomes Evaluated†	3 Treatment tolerance 9 Quality of life 6 Symptoms 6 Functional status

Abbreviation: KQ=Key Question.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Three studies evaluated standardized intensive nutrition counseling. One compared intensive nutrition counseling following the standard nutrition protocol of the Academy of Nutrition and Dietetics (AND) versus patients who received routine education across multiple cancer types during and after radiotherapy.[101] One study compared intensive nutrition counseling following a predetermined standard nutrition protocol (medical nutrition therapy protocol of AND) versus usual care in patients with cancers of the gastrointestinal tract and head and neck undergoing radiotherapy.[92] Finally, one study examined individual sessions with a dietitian (aimed at increasing soluble fiber and decreasing lactose in the diet) through 8 weeks of radiation therapy, versus standard care, in individuals with prostate cancer.[91]

Another group of studies evaluated individualized nutrition counseling or face-to-face interviewing. One included patients with colorectal cancer undergoing radiotherapy,[98] while the second also included colorectal cancer patients, but they were undergoing chemotherapy.[102] A third study compared dietary advice consisting of face-to-face interviews conducted during

chemotherapy in patients across multiple cancer types.[99] Another study compared guideline-based nutrition education counseling based on the patient's Patient-Generated Subjective Global Assessment score versus no nutrition education in patients undergoing radiation therapy across multiple cancer types.[103] Finally, one study evaluated the effect of face-to-face dietary counseling before chemotherapy sessions among individuals with breast cancer.[242]

The remaining studies were more diverse. One compared a standardized dietary advice approach for foods to avoid or consume in patients with prostate cancer undergoing radiotherapy.[96] One study compared a whole-course nutrition management model versus a general nutrition method for patients with gastrointestinal cancer undergoing chemoradiotherapy.[97] One study compared medical nutrition therapy that consisted of individualized dietary planning, nutrition education, as well as pharmacotherapy versus general nutrition advice in patients with gastrointestinal cancer undergoing chemoradiation.[94] A final study evaluated the Eating as Treatment (EAT) program which is based on motivational interviewing and cognitive behavioral therapy. Participants in this study were undergoing radiation for head and neck cancer.[90] Studies were not U.S.-based; most were conducted in Europe and Asia.

Dietary Supplements

Eligible Studies

Table 8.3 summarizes the characteristics of the literature set. We identified ten unique studies that examined dietary supplements initiated prior to or during cancer treatment and evaluated the impact of the intervention on symptoms.[26, 47, 55, 59, 115-117, 129, 131, 133] Over half of the studies enrolled 100 or more individuals, and while most studies assessed the impact of the nutrition intervention on clinical outcomes, other outcomes, such as symptoms (nausea and fatigue), body weight loss, quality of life, and treatment tolerance were also included. Other studies examined multiple outcomes but were less clear on the primary intent. Most studies (n=5) enrolled individuals with gastrointestinal cancers. Dietary supplements were prescribed by a dietitian/nutritionist in only two study, and less than half of the study populations were treated predominantly with chemotherapy. Appendix F provides detailed evidence tables.

Table 8.3. Basic characteristics of studies of effect of nutrition interventions on symptoms: dietary supplements

Characteristics	Information
Total Included Studies	10 Studies
Study Sample Size	3 50-75 1 76-100 6 >100
Cancer Type	1 Head & Neck 5 Gastrointestinal 3 Multiple cancers 1 Other cancer types*
Intervention Delivery Setting	3 Inpatient 4 Outpatient 2 Other 1 Not reported
Dominant Cancer Treatment Type of Participants	2 Surgery alone 4 Chemotherapy alone 3 Multiple therapies 1 Not reported

Characteristics	Information
Limited to Malnourished Patients	2 Yes 8 No
Malnourishment Screening Tool Used	1 MUST 3 Other tool/metric 1 Multiple tools 5 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 1 Nurse 1 Physician 1 Multiple providers 5 Not reported
Route of Administration	7 Oral 2 Enteral 1 Parenteral
Geographic Region of Intervention	3 Europe 6 Asia 1 North America
% of Participants with Stage IV Disease	1 10-25% 5 75-100% 4 Not reported
% Female Participants	2 0-25% 6 26-50% 1 76-100% 1 Not reported
Mean Age of Participants	6 <65 2 ≥65 2 Not reported
KQ3 Outcomes Evaluated*	2 Treatment tolerance 7 Quality of life 5 Symptoms 2 Functional status

Abbreviation: KQ=Key Question.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung).

Description of Interventions

Studies examined various types of supplements administered, timing, and route of administration, and comparators. Almost all of the studies included a measure of quality of life,[47, 115-117, 129, 131] while fewer investigated cancer treatment symptom relief,[117, 129] treatment tolerance,[47, 59] or functional status.[59, 115]

Seven studies examined a single supplement. Interventions varied by population with a wide range of durations and treatment contexts. One study compared supplementation with omega-3-fatty-acid-enriched nutrition versus a placebo while participants received chemotherapy for gastrointestinal cancer.[116] Another study compared an oral nutrition supplement with an eicosapentaenoic acid (EPA)-enriched supplement versus a standard diet for a population with multiple cancers.[115] A third examined an orally administered amino acid jelly, Inner Power®, for 21 days among breast cancer patients undergoing chemotherapy.[117] Another compared a glutamine injection plus total parenteral nutrition (TPN) versus TPN alone for individuals with advanced gastric cancer undergoing chemotherapy.[131] One study compared nutrition counseling only versus nutrition counseling with oral whey protein supplementation for 3 months in malnourished advanced cancer patients.[47] A single study compared amino acid supplements 1 week prior and for 5 weeks during chemotherapy versus standard care for gastrointestinal

cancer.[59] Finally, a five-arm study evaluated the combinations of EPA, l-carnitine, thalidomide, and medroxyprogesterone acetate/megestrol acetate (MA) for up to 4 months in individuals with cancer cachexia across different tumor types.[129]

Three studies examined multiple supplements to improve cancer treatment-related symptoms. One study investigated perioperative oral protein supplementation rich in arginine and omega-6 versus placebo in patients with gastrointestinal cancer undergoing surgery.[55] Another study compared and oral immunonutrition formula with fatty acids, arginine, fiber, and nucleotides versus a standard enteral formula in head and neck cancer patients undergoing chemotherapy.[26] The final study compared medium chain triglycerides and protein-enriched enteral nutrition, Nutrison® MCT, versus standard enteral nutrition for 5 days after surgery for gastrointestinal cancer.[133]

Special Diets

Eligible Studies

Table 8.4 summarizes the characteristics of the literature set. We identified 10 unique studies across 11 publications that examined the effects of special diets prior to or during cancer treatment on treatment-related symptoms.[139-147, 243, 244] The majority of studies enrolled patients with cancers other than gastrointestinal cancer, such as breast cancer[142, 143] and gliomas.[146] 60 percent of the studies enrolled more than 100 participants. Only two studies reported that the intervention had been administered by a dietitian/nutritionist, and one was administered by a physician. Almost all studies assessed quality of life and symptom status, with fewer assessing the impact of the intervention on functional status. Appendix F provides detailed evidence tables.

Table 8.4. Basic characteristics of studies of effect of nutrition interventions on symptoms: special diets

Characteristics	Information
Total Included Studies	10 Studies
Study Sample Size	1 50-75 3 76-100 6>100
Cancer Type	1 Gastrointestinal 2 Multiple 7 Other cancer types*
Intervention Delivery Setting	2 Inpatient 7 Outpatient 1 Not reported
Dominant Cancer Treatment Type of Participants	5 Chemotherapy alone 2 Radiation alone 1 Surgery alone 2 Multiple therapies
Limited to Malnourished Patients	10 No
Screening Tool Used	10 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 1 Physician 1 Other 6 Not reported
Route of Administration	9 Oral 1 Other
Geographic Region of Intervention	3 North America 3 Europe 3 Asia 1 Other

Characteristics	Information
% of Participants with Stage IV Disease	1 0-10% 1 26-50% 1 100% 7 Not reported
% Female Participants	1 26-50% 2 51-75% 5 76-100% 2 Not reported
Mean Age of Participants	6 <65 2 ≥65 2 Not reported
KQ3 Outcomes Evaluated†	7 Quality of life 7 Symptoms 3 Functional status

Abbreviation: KQ=Key Question.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Two studies evaluated the use of specific drinks. One compared the use of a glass of wine before eating along with additional oral nutrition support, such as Boost® or Ensure®, for 3 to 4 weeks during treatment for advanced cancer, versus oral nutrition support supplementation alone.[141] Another compared grape juice versus placebo prior to meals for one week following each of four cycles of chemotherapy.[140]

Another four studies examined fasting or calorie restriction. One study compared a ketogenic diet for 3 months versus standard diet in women with metastatic breast cancer undergoing chemotherapy,[142, 143] while the second compared a fasting mimicking diet versus standard diet at the initiation of chemotherapy for breast cancer.[144] The third study compared a calorie restricted ketogenic diet and fasting versus a calorie unrestricted diet for recurrent gliomas during radiation therapy.[146]A final study compared calorie restriction with synbiotics versus placebo to evaluate the impact on quality of life in women with breast cancer.[244]

The remaining studies examined modified diets by consistency or contents. One study compared early initiation of a solid versus liquid diet after surgery for gastrointestinal cancer.[145] A second study compared a diet containing no raw fruits or vegetables (cooked diet) versus a diet containing fresh fruits and vegetables for individuals undergoing induction therapy for acute myeloid leukemia.[139] A third study evaluated use of ginger on chemotherapy-induced nausea and vomiting in women with breast cancer.[243] Finally, one study compared a low-fat, modified-fat, and a normal-fat diet in individuals undergoing radiation therapy for pelvic malignancies.[147] Most of these studies were conducted in North America, Europe, and Asia. Overall, studies evaluating special diets varied in approach, populations, cancer treatments, and comparators.

Route or Timing of Nutrition Interventions

Eligible Studies

Table 8.5 summarizes the characteristics of the literature set. We identified eight studies that examined whether the route or timing of nutrition interventions delivered, at least in part, during cancer treatment, affected cancer or cancer treatment-related symptoms.[63, 68, 69, 153, 166, 168, 171, 172]

Half of the studies enrolled over 100 individuals. The majority of these studies examined adverse events[166, 168, 171, 172] and length of hospital stay.[166, 171, 172] Almost all studies enrolled individuals with gastrointestinal or head and neck cancers. Nutrition interventions were delivered by a dietitian/nutritionist in one study. The primary cancer treatment was surgery alone. Appendix F provides detailed evidence tables.

Table 8.5. Basic characteristics of studies of effect of nutrition interventions on symptoms: route or timing of nutrition interventions

Characteristics	Information
Total Included Studies	8 Studies
Study Sample Size	1 50-75 3 76-100 4 >100
Cancer Type	4 Gastrointestinal 2 Head and neck 1 Multiple cancer types 1 Other cancer types*
Intervention Delivery Setting	5 Inpatient 2 Multiple settings 1 Not reported
Dominant Cancer Treatment Type of Participants	5 Surgery alone 3 Multiple therapies
Limited to Malnourished Patients	1 Yes 6 No 1 Not reported
Malnourishment Screening Tool Used	1 Nutrition Risk Screening NRS-2002 1 Other tool/metric 1 Multiple tools 5 Not reported
Provider Prescribing or Delivering the Intervention	1 Dietitian/nutritionist 1 Physician 2 Multiple 4 Not reported
Route of Administration	3 Oral 1 Parenteral 3 Enteral 1 Other
Geographic Region of Intervention	4 Asia 1 Europe 1 North America 2 Other
% of Participants with Stage IV Disease	2 <10% 1 10-24% 1 25-49% 2 50-74% 2 Not reported
% Female Participants	2 0-24% 1 25-49% 1 50-74% 2 75-100% 2 Not reported
Mean Age of Participants	6 <65 1 65+ 1 Not reported
KQ3 Outcomes Evaluated†	2 Treatment tolerance 6 Quality of life 1 Functional status 1 Symptoms

Abbreviation: KQ=Key Question.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung). †Studies may evaluate multiple outcomes.

Description of Interventions

The eight studies identified varied in duration of intervention, comparator, cancer therapy received, and primary outcomes. Of the eight studies, four compared early oral feeding versus enteral nutrition. One study evaluated esophageal cancer patients after minimally invasive esophagectomy and compared early oral feeding compared to a nasoenteral feeding tube.[171] Another investigated early oral feeding compared to a nasogastric tube in patients who underwent elective colorectal resection.[153] A third study compared immediate initiation of enteral nutrition, after placement of a prophylactic gastrostomy tube, that continued through the completion of treatment versus standard care, which included initiation of enteral nutrition when indicated (e.g., oral intake <60% of estimated energy requirements).[71] Finally, a four-arm study compared combinations of predominately oral immunonutrition 7 days pre- and postoperatively versus standard nutrition support (Nestle Health Science) in individuals with esophageal cancer.[68]Another study examining timing of nutrition supplementation consisted of three arms and included patients undergoing elective surgery for breast and colorectal cancers. This study compared consumption of a milk-based oral nutrition supplement preoperatively and ending supplementation at either discharge or 90 days post-discharge.[69]

The remaining studies were more varied but focused on evaluating the mode of nutrition interventions on symptoms of cancer treatment. One study compared a percutaneous endoscopic gastrostomy tube versus a nasogastric tube in head and neck cancer patients undergoing curative treatment including radical surgery with adjuvant radiotherapy, chemoradiotherapy, or concurrent chemo- and radiation therapy.[168] Another study examined the use of jejunostomy feeding or nasogastric feeding in patients after a minimally invasive McKeown esophagectomy.[172] Finally, one study compared total parenteral nutrition versus an oral diet in breast cancer patients undergoing high-dose chemotherapy and hematopoietic cell transplantation.[166]

Nutrition Support Including Oral Nutrition Supplements

Eligible Studies

Table 8.6 summarizes the characteristics of the literature set. We identified 32 studies across 34 publications that examined the effect of nutrition support interventions during cancer treatment on cancer treatment-related symptoms.[33, 35, 37, 40, 42, 74, 78, 81, 85, 182, 184, 185, 187, 190-192, 195-197, 206, 208, 209, 213-216, 219-224, 228, 229] Studies varied in sample size, with just over half enrolling more than 100 participants. The primary intent of these studies also varied considerably, including biomarkers of nutrition status,[42, 216] inflammatory mediators,[74] feeding tolerance rate,[35] body weight changes,[190, 206, 222, 223] and quality of life,[191, 220] among others. While not the primary intent of most studies, almost all evaluated quality of life. Most studies were in gastrointestinal patients (n=20). Studies sometimes indicated that the intervention was delivered by a dietitian/nutritionist (n=7), and primary cancer treatments varied substantially across the studies. Appendix F provides evidence tables.

Table 8.6. Basic characteristics of studies of effect of nutrition interventions on symptoms: nutrition support including oral nutrition supplements

Characteristics	Information
Total Included Studies	32 Studies
Study Sample Size	6 50-75 11 76-100 15 >100
Cancer Type	5 Head and neck 20 Gastrointestinal 3 Multiple cancers 4 Other cancer types*
Intervention Delivery Setting	13 Inpatient 12 Outpatient 1 Multiple settings 4 Other 2 Not reported
Dominant Cancer Treatment Type of Participants	15 Surgery alone 4 Chemotherapy alone 2 Radiation alone 11 Multiple therapies
Limited to Malnourished Patients	7 Yes 25 No
Malnourishment Screening Tool Used	10 Nutrition Risk Screening NRS-2002 2 Multiple tools 7 Other tools/metrics 13 Not reported
Provider Prescribing or Delivering the Intervention	7 Dietitian/nutritionist 1 Physician 10 Multiple providers 14 Not reported
Route of Administration	23 Oral 4 Enteral 5 Parenteral
Geographic Region of Intervention	10 Europe 19 Asia 3 Other
% of Participants with Stage IV Disease	14 ≤10% 2 11-50% 5 51-75% 1 76-100% 10 Not reported
% Female Participants	7 0-25% 18 26-50% 5 51-75% 1 76-100% 1 Not reported
Mean Age of Participants	19 <65 7 ≥65 6 Not reported
KQ 3 Outcomes Evaluated†	7 Treatment tolerance 20 Quality of life 13 Symptoms 9 Functional status

Abbreviation: KQ=Key Question.

*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung).

†Studies may evaluate multiple outcomes.

Description of Interventions

Although all studies examined nutrition support, studies varied in the type and duration of such support as well as in comparators and cancers studied. Overall, studies fell into three general categories: oral or enteral nutrition before or after surgery, oral or enteral nutrition during chemotherapy and/or radiation, and total parenteral nutrition across cancer treatments.

Oral or Enteral Nutrition Before or After Surgery

Fifteen studies examined oral or enteral nutrition support before or after cancer surgery; the studies varied in the route and contents of nutrition support delivered, and the timing of the intervention and comparison groups. Eight studies delivered oral or enteral nutrition preoperatively. One study compared a carbohydrate-rich beverage in the 2 days prior to surgery for colorectal cancer versus preoperative fasting.[40] Another examined the use of peripheral intravenous nutrition on typically fasting days for patients undergoing in-hospital workup for biliopancreatic mass lesions.[37] Additionally, one study compared a single-dose versus a double-dose of a 10-percent glucose solution prior to radical gastrectomy.[33] Another study compared preoperative oral supplementation versus preoperative dietary advice for individuals undergoing surgery for gastrointestinal cancer.[35] A fifth study compared preoperative oral nutrition versus no oral supplementation in patients undergoing elective resection of colorectal carcinoma.[42] Another study investigated both pre- and postoperative early oral feeding versus conventional fasting in elderly patients with hepatocellular carcinoma.[74] Additionally, one study investigated an immune-enhancing diet versus a hospital-prepared blenderized diet 7 days before the operation and 14 days after in head and neck cancer patients.[85] Finally, one examined a whole oral nutrition supplement not enriched with immunonutrients 2 weeks prior to surgery and from preoperative days 2 to 14 among individuals undergoing gastrectomy versus unspecified standard care.[78] The remaining studies were delivered after cancer treatment began. While most interventions were delivered to head and neck and gastrointestinal cancer patients, one was assessed in women with gynecologic cancer.[182] Additionally, standard nutrition support was evaluated for a wide range of intervention lengths from 2 days prior[40] to 1,[187, 223] 2,[191] 3,[209, 228, 230] and 6[213] months postsurgery.

Oral or Enteral Nutrition During Chemotherapy and/or Radiation

Thirteen studies examined oral or enteral nutrition support before or after chemotherapy and/or radition; however, they varied in the route and contents of nutrition support delivered and the timing of the intervention and comparison groups. One study compared amino acid-enriched oral nutrition support 1 week prior to the start of chemoembolization for up to 1 year versus usual diet among individuals with hepatocellular carcinoma.[81] Two studies examined EPA-enriched oral nutrition support, but varied in populations, including lung[216] and multiple types of advanced cancer.[197] Another three studies evaluated hyperprotein-enhanced oral nutrition support,[190, 229] Immax®, and omega-3 fatty acid-enriched nutrition oral support for diverse populations and durations.[185] One study investigated standard nutrition support for the duration of chemotherapy in patients with gastrointestinal cancer.[219] One study examined standard nutrition support for the duration of radiation for patients with head and neck [192] and colorectal cancer.[98] Tree studies examined nutrition support during combined chemoradiation. Of these, one compared oral nutrition support, Niufutai®, for the duration of chemoradiation versus regular diet in individuals with advanced head and neck cancer.[195] The other two studies examined nutrition support versus dietary advice in individuals undergoing chemoradiation.[206,

[224] A final study compared early enteral support with chemotherapy versus only chemotherapy in gastric cancer patients after a radical gastrectomy.[221] Total Parenteral Nutrition

Four studies examined TPN across cancer and treatment types. One study compared oral feeding supplemented by TPN versus oral feeding alone in individuals with advanced cancer cachexia who were undergoing or had recently completed cancer treatment.[184] A second study compared TPN, Olimel®, for 4 to 8 days postsurgery versus isotonic fluids in individuals with gastric cancer.[196] A third study compared TPN, Nutriflex®, versus standard diet for 5 days postoperatively in individuals undergoing bladder cancer surgery.[220] A final study examined the use of TPN plus enteral nutrition support, Nutrison®, for approximately 7 days postsurgery for esophageal cancer versus enteral nutrition support alone.[222]

Multi-Component Interventions

Eligible Studies

Table 8.7 summarizes the characteristics of the literature set. Seven studies across eight publications examined multi-component nutrition interventions administered before or during cancer treatment.[88, 232, 234, 236, 237, 239, 240, 245] While the primary intent of the studies was to assess biomarkers of immune and nutrition status,[232, 239, 240] body weight changes,[234, 236, 237] symptoms,[245] and survival,[88] most also evaluated quality of life. Three studies enrolled over 100 participants. Studies varied in cancer populations, and interventions were most often delivered or prescribed by a dietitian or nutritionist. Most studies were conducted outside of the United States. Appendix F provides detailed evidence tables.

Table 8.7. Basic characteristics of studies of effect of nutrition interventions on symptoms: multi-component interventions

Characteristics	Information
Total Included Studies	7 Studies
Study Sample Size	2 50-74 2 75-100 3 >100
Cancer Type	2 Head and neck 3 Multiple cancers 2 Other cancer types*
Intervention Delivery Setting	6 Outpatient 1 Multiple settings
Dominant Cancer Treatment Type of Participants	1 Surgery alone 3 Chemotherapy alone 1 Radiation therapy 1 Multiple therapies 1 Not reported
Limited to Malnourished Patients	3 Yes 4 No
Malnourishment Screening Tool Used	2 Nutrition Risk Screening NRS-2002 2 Other tool 3 Not reported
Provider Prescribing or Delivering the Intervention	6 Dietitian/nutritionist 1 Multiple
Route of Administration	5 Oral 1 Other 1 Enteral
Geographic Region of Intervention	1 Asia 5 Europe 1 North America

Characteristics	Information
% of Participants with Stage IV Disease	1 <10% 1 51-75% 5 Not reported
% Female Participants	2 0-25% 3 26-50% 1 51-75% 1 76-100%
Mean Age of Participants	3 <65 4 ≥65
KQ3 Outcomes Evaluated†	6 Quality of life 3 Symptoms 2 Functional status

Abbreviation: KQ=Key Question.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).
†Studies may evaluate multiple outcomes.

Description of Interventions

Multi-component intervention studies varied in the type of interventions, comparators, cancer type, and cancer treatments delivered. Two studies examined individualized diet or nutrition plans combined with additional interventions such as education or counseling. One study examined nutrition counseling with individualized nutrition plans in individuals undergoing chemotherapy for multiple cancers.[234] The other study compared an individualized nutrition plan including nutrition counseling and dietary interventions such as oral nutrition support or protein rich snacks for 3 months versus standard care in individuals with cancer.[240]
The remaining studies varied widely in the types of interventions delivered. One three-arm study compared 1) a calcium-rich diet, 2) a calcium-rich diet plus exercise, and 3) a calcium-rich, low-fat and high-fruit-and-vegetable diet plus exercise in women with breast cancer undergoing chemotherapy.[232] Another three-arm trial compared dietary advice plus a supplement prior to chemotherapy versus dietary advice or no intervention in individuals with lung cancer.[88] A third study compared in-hospital nutrition education, early enteral nutrition support (24 hours after surgery), that continued 6 weeks postoperatively versus regular enteral nutrition support (48 hours after surgery) in individuals treated for laryngeal cancer.[239] Finally, one study compared a prophylactic percutaneous endoscopic gastrostomy (PEG) tube for early enteral feeding along with nutrition advice versus standard care in patients undergoing treatment for head and neck cancer.[236, 237]

Risk of Bias and Outcome Assessment

Table 8.8 summarizes risk of bias assessments. Appendix F provides risk of bias assessments and outcomes.

Table 8.8. Risk of bias assessment for nutrition interventions on symptoms

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types*
Nutrition Counseling	-	-	-	-
Dietary Supplements	-	3 Medium 2 High (N=5)	-	-
Special Diets	-	-	-	-

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types*
Route or Timing of Nutrition Interventions	-	-	-	-
Nutrition Support Including Oral Nutrition Supplements	-	5 Low 4 Medium 11 High (N=20)	-	-
Multi-Component Interventions	-	-	-	-

Abbreviation: - = risk of bias not performed.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung).

Outcomes for Dietary Supplements

Two of the three medium-risk-of-bias studies examined inpatient dietary supplementation, one with probiotics plus omega-3-fatty-acid-enriched nutrition in gastrointestinal cancer versus a placebo while participants received chemotherapy,[116] while another examined the use of a triglyceride and protein-enriched enteral nutrition in surgically treated patients with gastrointestinal cancer.[133] The third medium-risk-of-bias study examined protein-rich dietary supplementation at home and postoperatively for gastrointestinal surgery,[55] Study sample sizes ranged from 71 to 229 patients. Two studies reported on quality of life and symptoms, but the studies were distributed across interventions that could not be aggregated. One study of probiotics and omega-3 fatty acids reported improvement in quality of life.[116] The other study examining quality of life reported no benefit.[55] The two studies reported mixed outcomes for patient-reported symptoms with one reporting a benefit[116] and one no difference.[133]

Outcomes for Nutrition Support (Including Oral Nutrition Supplements)

Five low- and four medium-risk-of-bias study examined nutrition support interventions in the surgical inpatient setting.[33, 35, 40, 42, 74, 208, 209, 222, 223, 228] Study sample sizes were midrange, from 50 to 353. Treatment tolerance, quality of life, symptoms and functional status were reported in one to five studies, but these studies were distributed across interventions that could not be aggregated. The studies reported mixed results. Two low-risk-of-bias studies reported improvement in nausea[74, 208] and one reported improvement of functional status for individuals receiving preoperative oral carbohydrate drinks.[40] A second low-risk-of-bias study reported improvement in treatment tolerance and symptoms after use of oral nutrition supplements and dietary advice.[208, 209] One low- and one medium-risk-of-bias study reported no improvement in symptoms after increased preoperative oral supplementation.[33, 35] Another medium-risk-of-bias study reported no difference in quality of life or functional status after use of oral nutrition supplements after hospital discharge.[228]

Variation in the Effects of Nutrition Interventions on Preventing Negative Outcomes

While studies enrolled individuals from multiple cancer types, treatments, and stages (KQ3a), across the lifespan (KQ3b), with varying degrees of muscle wasting (KQ3c) and in those with a range of comorbid conditions (KQ3d), no eligible studies specifically evaluated

whether the effects of nutrition interventions on preventing negative outcomes varied across these characteristics.

Chapter 9. Effect of Nutrition Interventions Intended for Body Weight Loss

Key Points

- Four studies reported the effects of nutrition interventions intended for body weight loss using special diets among individuals with breast cancer.
- All studies assessed body weight and composition changes. One study reported on each of the following symptoms: quality of life, symptoms, and treatment tolerance.
- Studies showed high heterogeneity across study populations, interventions, and outcomes, making meta-analysis infeasible.

Overview

This chapter includes studies that addressed Key Question (KQ) 4 and examined the effect of nutrition interventions aimed at body weight loss for preventing and treating negative outcomes of cancer and cancer treatment in patients who are overweight or obese. We identified only four studies evaluating KQ4 (Table 9.1) and present a brief description of this limited literature set. Due to the small number of studies, we did not assess risk of bias. Detailed information on both studies can be found in Appendix G.

Table 9.1. Studies of effect of nutrition interventions intended for body weight loss, stratified by intervention type and cancer type

Intervention	Head and Neck	Gastrointestinal	Multiple Cancers	Other Cancer Types*	Total
Nutrition Counseling	0	0	0	0	0
Dietary Supplements	0	0	0	0	0
Special Diets	0	0	0	4	4
Route or Timing of Nutrition Interventions	0	0	0	0	0
Nutrition Support Including Oral Nutrition Supplements (Nutrition support)	0	0	0	0	0
Multi-Component Interventions	0	0	0	0	0
Total	-	-	-	-	4

Abbreviations: - = Not applicable.
*Other cancer types include studies evaluating all remaining cancer types not included in previous categories (e.g., breast, prostate, lung cancer).

Special Diets

Eligible Studies

Table 9.2 summarizes the characteristics of the literature set. We identified four unique studies examining the use of special diets prior to or during cancer treatment intended for weight loss.[244, 246-248]

Table 9.2. Basic characteristics of studies of effect of nutrition interventions intended for body weight loss: special diets

Characteristics	Information
Total Included Studies	4 Studies
Study Sample Size	2 76-100 2 >100
Cancer Type	4 Other
Intervention Delivery Setting	3 Outpatient 1 Other
Dominant Cancer Treatment Type of Participants	2 Chemotherapy 2 Multiple therapies
Limited to Malnourished Patients	2 No
Screening Tool Used	4 Not reported
Provider Prescribing or Delivering the Intervention	2 Dietitian/nutritionist 1 Multiple 1 Not reported
Route of Administration	4 Oral
Geographic Region of Intervention	2 Europe 2 Asia
% of Participants with Stage IV Disease	4 <10%
% Female Participants	4 76-100%
Mean Age of Participants	4 <65
Outcomes Evaluated	4 Body weight/composition changes

Description of Interventions

One study compared the effect of calorie restriction with synbiotics on quality of life and edema reduction in overweight and obese (body mass index between 25 and 35 kg/m^2) individuals with breast cancer-related lymphedema versus no intervention.[244] A second study compared the use of a diet designed to prevent weight gain versus control in women undergoing adjuvant chemotherapy for breast cancer who were close to being classified as overweight (average body mass index of 24.7 kg/m2) and were potentially at risk for body weight gain, particularly among women treated with cyclophosphamide, methotrexate, and fluorouracil (CMF).[246] Another study investigated the effect of a Mediterranean diet and dietary advice compared to only dietary advice on patients undergoing chemotherapy for breast cancer.[248] The final study compared intermittent 25-percent energy restriction versus continuous 25-percent energy restriction in breast cancer patients undergoing chemotherapy.[247] One study was conducted in Iran, one in Italy, one in South Korea, and one in England.

Chapter 10. Cost-Effectiveness of Nutrition Interventions

Key Points

- Among studies evaluating effectiveness of nutrition interventions, less than 4 percent published any cost information related to the intervention. These studies were predominantly conducted in inpatient settings in non-U.S. health systems.
- In the grey literature, few studies conducted cost-effectiveness or cost-benefit analyses, but those that did demonstrated mix results on the value (cost-benefit, cost-effectiveness) of nutrition interventions in non-U.S. health systems.

Cost-Effectiveness

This chapter provides an overview of the literature set addressing the Contextual Question of cost-effectiveness of nutrition interventions for cancer. As noted in the methods, we took a broad approach to evaluate this contextual question and studies that evaluated the cost or value (e.g., cost-effectiveness, cost-benefit) of nutrition interventions for cancer. Among the literature set included in the Key Questions (n=206), fewer than 4 percent (n=8/206) of studies published any information on the cost of the nutrition intervention. Many times, the cost-related information was focused on the total cost of care for one group versus a comparison group, making it challenging to identify the exact cost of the intervention or its components. When cost information was provided, studies were often performed outside of the United States, including in Europe and Asia (Table 10.1). Within each intervention type where cost information was provided, study populations, timing, and duration of the interventions as well as the interventions themselves were very heterogeneous. All but one study evaluated costs in the inpatient setting.

Table 10.1. Summary of literature evaluating Contextual Question on intervention cost or cost-effectiveness

Study	Intervention/ Control	Cost of Nutrition Intervention	Costs Broken Down by Intervention Components?	Formal Cost-Effectiveness Done?	Setting and Location of Intervention
Braga 2001[151] Key Question 2	TPN / EEN	Cost per day TPN: $90.60 vs EEN: $25; (p < .001) (Denomination: US Dollars)	Yes Prescriptions: 73.2% of TPN costs vs. 22% of EEN costs; Monitoring and personnel costs similar between two groups	No	Inpatient Italy

Study	Intervention/ Control	Cost of Nutrition Intervention	Costs Broken Down by Intervention Components?	Formal Cost-Effectiveness Done?	Setting and Location of Intervention
Gianotti 2000[249]	Perioperative enteral immunonutrition/ Standard enteral diet	Cost per group: Perioperative: 35,437 Standard: 10,768 ; (Denomination: Euro)	No	Yes Cost-effectiveness: Net savings of 2,386 euros in the intervention per complication free patient	Inpatient Italy
Klek 2005[119] Key Questions 1&2	Intervention Group 1: PN+ omega 3 fatty acids; Intervention Group 2: PN+ glutamine; Control: standard PN	Mean cost of overall hospital stay with cost of PN removed: PN + omega 3 fatty acids: 3,360 PN + glutamine: 3,240 Standard PN: 3,720 No p-value reported (Denomination: Euros)	No	No	Inpatient Poland
Li 2015[204] Key Question 2	EN/ conventional perioperative treatment after gastric cancer surgery	Total hospital costs EN: 32 Conventional perioperative treatment: 35 P<0.01 (Denomination: US Dollars)	No	No	Inpatient China
Ryu 2009[167] Key Question 2	TPN/ (NGTN)	Per patient daily cost TPN group: 31,410 ($34.41) versus NGTN group 19,600 ($19.60) (Denomination: 2007 KRW)	Yes Nutrition: 28,320 (TPN) vs. 18,400 (NGTN); Personnel: 1,410 (TPN) vs. 1,200 (NGTN)	No	Inpatient Korea
Song 2017[239] Key Question 2,3	Hospital to home nutrition management model /routine nutrition management	Overall hospitalization costs: Hospital to home: 2.73 vs. Routine: 2.65, P=0.778 (Denomination: RMB)	No	No	Inpatient, Home China
Wang 2019[250] Key Question 2	EOF/ DOF after surgery	Overall hospitalization costs: EOF: 8.24 vs. DOF: 8.44, (p=0.492) (Denomination:10^4 yuan)	No	No	Inpatient China

Study	Intervention/ Control	Cost of Nutrition Intervention	Costs Broken Down by Intervention Components?	Formal Cost-Effectiveness Done?	Setting and Location of Intervention
Xiao-Bo 2014[176] Key Question 2	TPN/EN	TPN: 123 vs EN: 66, ($p<0.05$), unclear of included cost components (Denomination: Unknown)	No	No	Inpatient China

Abbreviations: DOF= delayed oral feeding; EEN= early enteral nutrition; EN=enteral nutrition; EOF= early oral feeding;.KRW= Korean Wan; NGTN=nasogastric tube nutrition; RMB: renminbi; PN=parenteral immunonutrition; TPN= total parenteral nutrition;

In a grey literature search (see Appendix A for methods), including search of the Tufts Cost Effectiveness Analysis Registry, we identified a few additional studies that performed formal cost analyses of nutrition interventions. Two studies conducted a cost-benefit analysis of preoperative immunonutrition from a randomized controlled trial included in our Key Questions. One cost-effectiveness analysis[251] demonstrated an economic advantage for those receiving preoperative immunonutrition relative to the conventional approach based on a randomized controlled trial of individuals undergoing surgery for gastrointestinal cancer.[66] Another study evaluated the cost-effectiveness[252] of results from a randomized controlled trial[185] examining oral nutrition supplements with nutrition counseling among those undergoing radiation therapy for head and neck cancer. This study showed that the intervention was less costly and more effective than nutrition counseling alone. However, there was high uncertainty around this estimate. One study examined the cost-effectiveness of perioperative enteral nutrition versus standard of care for colorectal cancer surgery, finding that the intervention resulted in an incremental cost-effectiveness ratio (ICER) of -6,276 Euros, with a marginal gain in quality adjusted life years.[253] An additional recent study evaluated the use of supplemental parenteral nutrition versus enteral nutrition alone and found that for patients with Stage IV inoperable pancreatic cancer the incremental cost-effectiveness ratio was 41,350 or 91,501 British Pounds depending on whether nursing or home delivery costs were combined or provided separately.[254] Finally, in a narrative review and economic analysis, one study examined the value of nutrition support in patients with gastrointestinal malignancies. The study identified published literature with cost and clinical outcomes and conducted a Value Analysis by developing models using Medicare claims from gastrointestinal cancer patients. The study concluded that application of nutrition interventions provides positive clinical and economic value to the health system for this population.[255]

In mixed populations (i.e., in studies that evaluate critically ill or hospitalized patients who possibly have cancer), a few additional resources might inform discussions on cost-effectiveness. One systematic review evaluated the cost effectiveness of using standard oral nutrition supplements in the hospital setting. The study identified eleven cost analyses, primarily comprising secondary analyses of randomized controlled trial data, that suggest standard oral nutrition supplements in the hospital setting produce a cost saving and are cost-effective.[256] Another study examined the cost savings associated with nutrition support in medical inpatients based on a systematic review of randomized trials, finding that for medical inpatients who are malnourished or at nutrition risk, in-hospital nutrition support offers a cost-effective way to reduce readmissions.[257] A third study evaluated the cost-effectiveness of omega-3-fatty-acid-enhanced parenteral nutrition versus standard parenteral nutrition in hospitalized patients, and showed that the intervention demonstrated superior clinical efficacy and decreased in mean

treatment costs.[258] Finally, one recent study examined the value of nutrition support therapy (including a sub analyses of gastrointestinal cancers), modeling the impact of adoption in the Medicare population, and concluded that optimization of nutrition support therapy for specific patient populations is estimated to reduce Medicare spending by millions of dollars per year.[259]

Chapter 11. Discussion

Overview

This evidence map sought to provide a broad overview of randomized trial evidence for the effectiveness of nutrition interventions delivered prior to or during cancer treatment for preventing and treating negative outcomes of cancer and cancer treatment. Strengths of our report include: a comprehensive search and inclusion of randomized control trials relevant to the topic; high-level mapping of the evidence across Key Questions by patient, intervention, comparator, and outcome categories; identification of evidence gaps; creation of an active evidence repository to facilitate future, more detailed, analyses of the included studies; development of an analytic framework to guide our review questions; categorizations of populations, interventions, cancer types, treatments, and outcomes of interest to support a fresh, rigorous, and independent organizational framing to an extremely broad field; targeted assessment of study methodological quality focused on intervention and cancer areas with the highest volume of identified evidence; and suggestions for new research based on our findings.

Our review identified, from a broad range of nutrition interventions (e.g., dietary supplements, nutrition support, nutrition counseling), the most commonly reported strategies or components and their outcomes relevant across populations, cancers and cancer treatments. Our results should help clinical experts, policymakers, and funding agencies to prioritize a research agenda related to the use of nutrition interventions in cancer treatment.

Overall, we found two decades of randomized trial evidence across more than 206 studies on nutrition interventions for adults prior to and/or during cancer treatment focused on the use of dietary supplements, nutrition support (including oral nutrition supplements), and the route or timing of nutrition interventions within gastrointestinal and head and neck cancers. Most studies examined changes in body weight/composition, adverse events, length of hospital stay, and quality of life. Among interventions with a high volume of literature, made up mostly of studies of dietary supplements and nutrition support in patients with gastrointestinal and head and neck cancers, 11 percent (n=12) were rated as low risk of bias (higher quality), 40 percent (n=46) medium risk of bias and 49 percent (n=56) high risk of bias (lower quality). Low- and medium-risk-of-bias studies reported mixed results on the effect of nutrition interventions across outcomes of cancer and cancer treatment.

Our review process aimed to identify nutrition interventions supported by evidence that met a minimum threshold of quality. Due to the diversity and volume of the literature, we intentionally focused risk of bias assessment within intervention and cancer types where we found a high volume of studies, as we note in our methods. We used this strategy in order to identify the greatest amount of lower risk of bias evidence for specific nutrition interventions by cancer types. These mainly focused on use of dietary supplements, nutrition support, and the route or timing of interventions. Even within this subset of 100 studies, heterogeneity of populations, interventions (e.g., type, amount, duration), and outcomes (not only outcomes, but when and how measures were assessed) mostly precluded our ability to aggregate findings. Further, this literature comprised mostly high risk of bias studies. Therefore, our findings point to the need for rigorous new research to bolster the evidence base. Our findings also suggest the need for more a detailed future assessment of studies contained in this evidence map. Such a future assessment could focus on priorities and interventions most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers), and therefore lead to studies

specifically designed to evaluate the main outcomes of interest relevant to the identified Key Questions. These results were presented to inform discussion of experts and stakeholders at the National Institutes of Health Pathways to Prevention Program (P2P) conference, held July 26th-28th, 2022. Based on this evidence, an independent panel developed a draft report to summarize the workshop discussions and identify specific future priorities, which can be found on the P2P Workshop website (https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/nutrition-prevention-improved-cancer-health-outcomes).

Broader Context of Available Interventions and Strategies

The contextual question addressed by our review examined the cost-effectiveness of nutrition interventions delivered prior to or during cancer treatment. However, few studies provided information on the cost of the interventions delivered or performed a formal cost-effectiveness analysis. The lack of cost-effectiveness literature in this topic area is not surprising. Research must first establish effectiveness of an intervention before cost-effectiveness can be addressed. However, as the literature matures to establish an evidence base for effectiveness of nutrition interventions, studies must provide sufficient information on the implementation of the interventions to allow for comprehensive cost-effectiveness analyses. Specifically, studies frequently reported only sparse details about added medical (e.g., supplies, technology, drugs) and personnel investments necessary to implement a given intervention. Additionally, when studies did report costs, they mostly did so in a summative way that lacked sufficient detail needed to identify which component(s) contributed to the overall intervention. Further, most cost information came from trials conducted outside of the United States, where costs of care and treatment contexts differ significantly from U.S. settings and therefore reduce applicability. Future research should emphasize not only effectiveness of interventions, but also the components of cost in a detailed manner applicable to the United States context.

Future Research

The question of if nutrition interventions (or components) can prevent negative health outcomes, and, for whom and under what circumstances is of vital importance. The number of individuals experiencing or at risk for cancer-related malnutrition remains substantial, with estimates ranging from 25 to 80 percent across patient populations.[8-10] Because cancer risk increases with age, the rapidly growing older population in the United States will increase demand for cancer care and, by extension, nutrition therapy, over the coming decades.[260] However, the topic of nutrition interventions to prevent adverse effects of treatments for cancer patients at risk for malnutrition is extremely broad. This breadth increases complexity for adequately addressing needed evidence. Although our report identified a great many studies, they differed widely by population, intervention type, intent, timing, and mode of delivery, as well as comparators, cancer types, treatments, and outcomes. Even within intervention categories, we found substantial heterogeneity, making aggregation infeasible. Importantly, many studies were not specifically designed to evaluate the main outcomes of interest relevant to the identified Key Questions. However, these findings should not serve to discourage, but rather bolster, the rigor and content of future research informing clinical practice on nutrition interventions for cancer, including expansion of investigations of the role of malnutrition screenings, which was not addressed by this review.

In the near term, research could evaluate evidence from existing methodologically rigorous observational studies. Our evidence map did not include such studies, but they could provide valuable information about the association between nutrition interventions and negative outcomes of cancer and cancer treatment. Further, observational studies could provide additional context on potential effectiveness when interventions are unethical to randomize or to describe the natural course of nutrition status and body composition changes over the course of treatment to identify individuals at risk for malnutrition. Ultimately, evidence maps scan the horizon of existing information, while providing a repository to facilitate a deeper assessment of the direction, magnitude, and certainty of intervention effects in high priority/high literature volume areas. Therefore, our map may provide the basis for a future quantitative assessment or more detailed stratification of our findings. Such an assessment could focus on the specific nutrition interventions, cancers, and cancer treatments most relevant to patients, clinicians, and guideline groups. Longer-term funding efforts, which should align with the priorities of the National Institutes of Health Precision Nutrition Initiative,[261] should also focus on 1) standardizing definitions and taxonomies for populations, interventions, and outcomes (including identifying those 'at-risk' for malnutrition), and 2) improving rigor in the design and reporting of nutrition interventions. To further expand on specific areas that could benefit from standardized definitions and improved rigor, we outline below several future research areas that could inform practice and policy.

Methodological Rigor

The literature included in this review represented an extremely broad and diffuse array of nutrition interventions delivered. Interventions ranged from short-term use of dietary supplements, many of which had minimum caloric value, to multi-month use of oral nutrition support (e.g., Ensure®). Such wide-ranging interventions may differ significantly in ability to address underlying malnutrition. Oftentimes, the literature lacked a clear conceptual model justifying how the intervention would be expected to improve outcomes. As a result, the field could benefit from development of a comprehensive and clear conceptual framework addressing how these diverse nutrition interventions fit within clinical pathways, as well as how they could improve key outcomes of most importance to stakeholders. Further, a detailed conceptual framework could outline potential mechanisms for the effect of nutrition interventions across patient nutrition risk categories, cancers, and cancer treatments. Such a framework could therefore help determine which areas are most likely to answer clinical questions and outcomes (rather than intermediate measures) that are of highest priority to clinicians and patients. Ultimately, this would help researchers prioritize, from the set of diverse interventions, those that conceptually might best address malnutrition in this population.

Additionally, although we limited our studies to include only randomized controlled trials with a minimum enrollment of ≥50 participants, we were struck by the lack of adherence to basic reporting standards for randomized controlled trials within these publications. Substandard reporting ranged from missing information on the randomization process, blinding of participants and assessors, and populations analyzed, among others. Therefore, the current literature base was largely categorized as having a high risk of bias due to conduct and reporting, most often due to lack of clarity around the performance (e.g., analyzing individuals as randomized, blinding of participants and assessors), and detection (e.g., ability to assess how outcomes were defined and evaluated). Funding and publication of future research on nutrition interventions should emphasize consistent use of criteria laid out in the CONSORT statement.[262] CONSORT

comprises a 25-item checklist and flow diagram focused on accurate and consistent reporting of how a trial was designed, analyzed and interpreted. Further, clear and complete reporting of research sponsorship is critical as several included studies that were funded (in part or whole) by organizations with the potential to influence findings. More widespread adoption of this tool may enhance the methodological rigor of the conduct and reporting of future published nutrition intervention studies, increasing the overall quality of the literature. Finally, we recognize that limiting to evaluation to only randomized controlled trials may not address the underlying issue of bias in access to and enrollment in clinical trials, with prior research demonstrating underrepresentation among key populations such as those from communities of color, the uninsured and those experiencing adverse social determinants of health.[263] Coupling strong methodological practices and reporting with coordinated efforts to inform research priorities could help to better focus resources on high priority areas with the greatest potential to improve outcomes and practice.

Populations

During topic refinement, stakeholders were eager to understand the available literature within specific populations of individuals receiving nutrition interventions (e.g., adults ≥65 years old, those with muscle wasting, individuals with comorbid conditions). Although the included literature may have enrolled individuals from these important subpopulations, studies rarely reported results according to these characteristics. Rather, studies tended to focus on very specific populations, such as individuals undergoing gastrectomy for early-stage gastric cancer. Results from such narrowly specific populations may not be broadly applicable or transferrable to interventions in other cancer populations or treatments. Additionally, many studies often used broad or relatively vague definitions for "at risk for malnutrition", ranging from defining all individuals with cancer diagnosis as having risk for malnutrition to using specific malnutrition screening tools (e.g., Nutrition Risk Screening (NRS)-2002), which were rarely reported in the literature. Other studies relied on body weight, weight loss, and body mass index as indicators of malnutrition. Such definitions cannot capture the comprehensiveness or complexity of malnutrition from a clinical, epidemiological, public health, or sociodemographic perspective including racial/ethnic disparities and food insecurity. These vague definitions of malnutrition made it difficult to assess and compare across studies the baseline need for nutrition interventions or opportunities for improvement in nutrition status, which should be consistently evaluated at baseline and post-intervention. Prior research examining malnutrition screening in well-defined populations has demonstrated it is feasible to identify and quantify individuals with cancer who are at risk for malnutrition using defined tools.[264] Future research should seek to more clearly define malnutrition and risk for malnutrition. Better definitions would make it easier to identify malnutrition and its root cause(s) as well the groups most likely to respond to specific interventions.

All but a few studies within this literature set focused on head and neck and gastrointestinal cancers. The focus of nutrition interventions within head and neck and gastrointestinal populations is not unexpected due to the higher risk of malnutrition in these populations due to a combination of changes to the digestive tract as a result of the cancer as well as functional changes resulting from the cancer treatments themselves.[265] This presents opportunities to evaluate within other cancer types to ensure that tested interventions are implemented in populations with the greatest need (i.e., highest risk for malnutrition) and burden (i.e., most common cancers). Additionally, as is common in randomized controlled trials, studies tended to

enroll younger populations (with mean ages at enrollment of <65 years) relative to the overall cancer population (with average age of diagnosis >65 years). Studies rarely reported race and ethnicity. Finally, almost all studies were conducted outside of the United States—mainly in Asia and Europe—where nutrition norms, costs of care and available resources differ greatly from the United States. While several ongoing studies registered on Clinicaltrials.gov hold potential to further inform the discussion on the effect of nutrition interventions and cancer such as DIANA-5 (NCT05019989), DEDiCa (NCT02786875), and MEDEA (NCT04304924), the majority of these studies are sponsored and conducted by non-U.S. institutions. To better inform future implementation, future research should examine the effects of interventions across populations and ensure they are applicable to United States settings to inform future implementation.

Intervention

Overall, we note significant diversity in the nutrition interventions tested to reduce the negative effects of cancer treatment and associated symptoms. Interventions were extremely heterogeneous, even within intervention types. For example, studies in dietary supplements included omega-3 fatty acids, glutamine or arginine, among others. Even when the studies used the same interventions, they varied dramatically in duration (e.g., 2 days versus 3 months), dosage, purity, route of administration, and type of cancer treatment received. Many of the interventions studied have little standardization even within agreed upon nutrition intervention categories. Further, we were often unable to ascertain specific features of the conduct of the trial such as detailed information on contents and modality of nutrition received in the interventions groups, the context of the settings (inpatient versus outpatient), and adherence. Additionally, few (<10%) studies specifically identified which nutrition professional prescribed or administered the intervention.

Comparison groups for studies also reflected heterogeneity, and varied in their use of comparisons to test different doses and types of the intervention against an all-encompassing "standard of care" that was often incompletely defined, if at all. Further, we often found it difficult to understand exactly what the comparison group received in terms of dose, duration or quantity of the nutrition intervention. In several cases, the nutrition interventions tested more than one variable at a time relative to the comparison group. For example, a study may have implemented a nutrition intervention later in the comparison group relative to the intervention and also calorie restricted the control group. These combined differences in the comparison group make it difficult to determine which factor(s) account for outcomes across groups. Study designs could be enhanced by complete reporting of total daily caloric intake across study groups. Finally, control group interventions for at-risk or malnourished adults should reflect current professional practice standards. Several non-US surgical studies used prolonged non-feeding postoperatively as a control, which was deemed unethical by several authors[62, 66, 150, 263] given recommendations of several professional societies more than two decades ago. Overall, heterogeneity in intervention type and reporting, and the resulting absence of key information, limited our ability to aggregate or conduct meta-analyses (beyond qualitative summaries) or accurately quantify risk of bias. Beyond the broad interventions themselves, studies rarely aimed nor were they statistically powered to examine variation in cancers studied or in types of healthcare providers. This made it difficult to determine the broader relevancy and applicability of findings from a given intervention for patients with a specific cancer (type/location/stage), treated in a selected setting (outpatient vs. inpatient) by different clinicians (surgeon, radiation

oncologist, oncologist). This may be particularly relevant among studies of individuals with advanced cancer, where body weight loss may no longer be a nutritional issue, but rather a metabolic issue that may be better treated pharmacologically.

The current evidence lacks overarching coordination based on a strong clinical foundation for effectiveness in preventing cancer treatment harms—a problem made worse by wide variation in cancer types, stages, symptoms, and treatment approaches. Comorbidities further complicate the picture, as does the relatively short duration of cancer treatments. The field needs to identify more comprehensive interventions and assess whether research should focus on specific cancer types/stages/treatments or use a more general approach across these areas. In other words, the field must determine if nutrition interventions are only effective in certain clinical situations or are more broadly applicable across cancer populations. Therefore, future research needs well-designed studies with detailed reporting on the interventions in settings and subgroups well aligned with priorities within U.S. settings and practice.

Outcomes

Outcomes collected to assess the impact of nutrition interventions were diverse and ranged from intermediate outcomes, such as changes in body weight, to longer-term outcomes such as changes in overall survival. We treated outcomes as a single category encompassing both outcomes of cancer and cancer treatment. We based this choice on the fact that the studies themselves did not differentiate between these outcome categories making it impossible for us to disaggregate them and assign to one category or the other.

Additionally, the fact that relevant outcomes were reported does not mean that these outcomes were the primary intent of the studies or that the studies were adequately powered to detect differences in specific outcomes. Qualitatively, in our data abstraction, we noted that many studies were focused on examining the impact of nutrition interventions on clinical laboratory markers of nutrition status or immune function; yet they also reported differences in mortality and length of hospitalization even though these were not stated as a primary, or even secondary, outcome. In addition, outcomes were often poorly defined, with few details provided on the timing or definitions of outcomes. While validated tools were sometimes used to quantify outcomes of interest, such as the Common Terminology Criteria for Adverse Events (CTCAE), more often studies only reported that an adverse event occurred. Studies reported few details on outcome evaluation (how, by whom, over what time frame and using what criteria the outcome was evaluated). Specifically, studies rarely reported differences in attrition or length of hospital stay/followup between the intervention and comparison groups. This presents particular challenges for outcomes such as adverse events, where the longer someone is observed, the more likely it is that outcomes of interest will be identified. Even when outcomes were clearly evaluated using validated tools, the tools selected (e.g., quality of life measures) varied across studies, making aggregation and comparison impossible.

One crucial way to improve outcome assessment in future nutrition intervention studies will be to use standardized assessments with common, validated tools coupled with clearly defined assessment time periods that are consistent between the intervention and comparison group. This may include routine data collection of dietary intake and other measure of nutrition status. Additionally, studies need to report how outcomes were assessed, by whom, and according to a standard *a-priori* criteria. Many of these components are encompassed more broadly within the CONSORT criteria. However, our review suggests opportunities for professional societies representing nutrition and oncology professionals to advance a minimum reporting set of

validated outcomes for nutrition intervention studies. However, we also recognize that collection of standardized, validated tools for assessment of the most clinically relevant outcomes must be balanced with the feasibility of collection (e.g., imaging, invasive biopsies) that promote recruitment of adequate sample sizes from diverse populations for these nutrition interventions.

Implementation and Systems Complexity

In addition to intervention related considerations, nutrition and oncology professionals, policymakers and payers should remain aware of potential implementation considerations. Even when high-quality evidence is advanced to support the use of specific nutrition interventions, implementation may be difficult for many reasons. First, most nutrition intervention studies have been conducted in Asia and Europe, raising questions about feasibility or practicality of implementing these interventions in U.S. settings, where practice considerations and norms differ. Second, the United States continues to under-resource nutrition professionals in both inpatient and outpatient settings,[266, 267] leading to poor overall access to comprehensive nutrition care for cancer patients across the United States[17] Introducing new or expanded nutrition interventions without also enhancing capacity to implement these interventions will be problematic. Reimbursement for nutrition interventions, particularly outside of the inpatient setting, remains sparse. Finally, because studies were conducted in research settings with selected volunteers, we do not know whether our findings are applicable to non-research settings. Our report did not address how social determinants of health affect malnutrition risk, or barriers and facilitators for reducing malnutrition or adverse effects of cancer treatment outcomes, all of which needs attention from future research. As a result, implementation of nutrition interventions will require comprehensive considerations of equity across populations with different underlying social determinants of health.

Once evidence is established for the effectiveness of nutrition interventions, additional resources and administrative support will be required to integrate these interventions into complex care systems. Some approaches for facilitating needed resources and support include value-based care models or medical homes that support innovative approaches to addressing and improving outcomes more broadly among individuals with cancer. These models may encourage use of effective supportive care interventions (including use of dedicated nutrition professionals, such as registered dietitians) to improve outcomes in this population. As with studies evaluating the effectiveness of the nutrition interventions themselves, these approaches must be coupled with rigorous research designs in future studies to ensure evidence-based implementation.

Research Approaches

Our evidence report identified areas that have implications for future research and by extension practice and policy. This review illustrates the breadth of the topic and exposes the complexity of obtaining high-quality needed evidence. One important step may be to develop a clear and detailed conceptual framework that addresses the clinical pathways involved in the care process. Such a framework would focus and clarify definitions of individuals “at risk for malnutrition.” It would encompass an extensive field of nutrition interventions that vary widely in delivery, composition, dose, and purity and standardization even within agreed upon nutrition intervention categories. The framework may address variation in cancers studied and cancer care providers. Importantly, this could help clarify the broader relevancy of findings from a given intervention administered in selected patients with a specific cancer (type/location/stage), treated

in a selected setting (outpatient vs. inpatient) by different clinicians (surgeon, radiation oncologist, oncologist). It could also serve to reinforce the value of patient-important and clinical outcomes over intermediate outcomes such as body weight or biochemical values. The framework would also place into context the role of social determinants of health (e.g., lack of access to insurance, economic and social stability, the built environment, social support) on the effects of nutrition interventions, particularly due to the lack of data on these factors in included studies.

Programmatic goals could target research toward support of large well designed randomized trials in high priority well-defined populations, using standardized nutrition interventions and delivery modes, and addressing cancers and cancer clinicians/treatments of interest and clinically relevant outcomes. Decisional dilemmas often revolve around whether to use broader statements of "what are the effects of nutrition interventions in cancer patients" or narrower "does a specific nutrition intervention delivered in a given way to a specific group of cancer patients treated in a certain setting by a given clinician ameliorate a selected negative outcome." And if the latter, what is the generalizability of the findings to other clinical situations?

Strengths and Limitations of the Review

We selected methods for this review that provided a detailed evidence map of the current state of literature on nutrition interventions, highlighting not only concentrations of literature but also gaps in intervention types. We used purposefully broad definitions of nutrition interventions, thereby increasing the scope, breadth and heterogeneity of the included literature to better assess the range and depth of available evidence. This decision allowed for demonstration of the diffuse literature set on the topic and highlighted the predominantly low quality of literature where there were concentrations of similar intervention types. However, this required focusing on high level directionality of intervention effects across a broader range of nutrition interventions rather than detailed, precise estimates of intervention effects. Overall, this approach allowed for high level mapping of the evidence across Key Questions by patient, intervention, comparator and outcome categories, which helped to identify evidence gaps for future research.

Conclusions

Overall, this evidence map of randomized controlled trials found great heterogeneity across populations, nutrition interventions, cancer types and treatments and outcomes. While this report identified a large number of studies, these studies examined a wide variety of populations, nutrition intervention types, intent, timing, and mode of delivery as well as comparators, cancer types and treatments, and outcomes. Additionally, heterogeneity within each of these factors precluded aggregation of results. The highest concentration of literature comprised mainly high-risk of bias studies. Importantly, few studies were specifically designed to evaluate the main outcomes of interest relevant to the identified Key Questions. In the relatively near term, future research could evaluate evidence from existing methodologically rigorous observational studies. We did not include such studies in our evidence map, but they might provide relatively rapid and valuable information of the association between nutrition interventions and cancer treatment outcomes. Additionally, mapping overviews serve mainly as a horizon scan of the existing information, while providing an evidence repository to facilitate a deeper assessment of the direction, magnitude, and certainty of intervention effects in high priority/high literature volume areas. Future research could involve a quantitative assessment or more detailed stratification of

findings for specific nutrition interventions, cancers, and cancer treatments (or across these categories) deemed most relevant to patients, clinicians, and guideline groups. Parallel efforts in the development of longer-term funding efforts should include a focus on creating standardized definitions and taxonomies for populations, interventions, and outcomes, as well as improved rigor in the design and reporting of nutrition interventions. Specifically, the field needs a more detailed future evaluation of a subset of nutrition interventions contained in this evidence map that focus on priorities most relevant to specific stakeholders (e.g., oncologists, patients, dietitians, researchers, policymakers). Currently, the quality and heterogeneity of the studies limit the ability to translate findings into clinical practice or guidelines. The field would benefit from coordinated efforts to develop detailed conceptual frameworks for mechanisms of nutrition interventions effects across patient nutrition risk categories, cancers, and cancer treatments. Such a framework would help determine those areas likely to answer clinical questions and outcomes (rather than intermediate measures) of highest priority to clinicians and patients. These frameworks can also help to prioritize research agendas as well as to inform study designs, and, ultimately clinical practice and health policy. Finally, this report did not address the relationship between social determinants of health and malnutrition risk, or relevant barriers and facilitators relevant to reducing malnutrition through nutrition interventions. Future research should examine the evidence relevant to these issues and effective interventions.

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Abbreviations and Acronyms

AE	adverse event
AND	Academy of Nutrition and Dietetics
AHRQ	Agency for Healthcare Research and Quality
BCAA	branched-chain amino acid
BMI	body mass index
BW	body weight
CFU	colony forming unit
CHO	carbohydrate
CINV	hemotherapy-induced nausea and vomiting
CMF	cyclophosphamide, methotrexate, and fluorouracil
CONSORT	CONsolidated Standards of Reporting Trials
CQ	contextual question
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease free survival
DHA	docosahexaenoic acid
EAT	Eating As Treatment program
EEN	early enteral nutrition
EEIN	early enteral immunonutrition
EN	enteral nutrition
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire
EPA	eicosapentaenoic acid
EPC	Evidence-based Practice Center
EPN	early parenteral nutrition
EQ-5D	EuroQol-5D
ER	emergency roomFA fatty acid
FFM	fat free mass
FM	fat mass
GLA	gamma-linolenic acid
HRQOL	health related quality of life
ICU	intensive care unit
IEN	immunoenteral nutrition
IMEN	immunomodulating enteral nutrition
IMPN	immunomodulating parenteral nutrition
ITT	intention-to-treat

IV	intravenous
KQ	Key Question
LCT	long chain triglyceride
LOS	length of hospital stay
MA	medroxyprogesterone acetate/megestrol acetate
MAC	mid-arm circumference
MAMC	mid-arm muscle circumference
MNA-SF	Mini Nutrition Assessment – Short Form
MST	malnutrition screening tool
MUST	malnutrition universal screening tool
NA	not available
NG	nasogastric
NI	nutrition intervention
NIDT	nutrition intervention during treatment
NIH	National Institutes of Health
NJT	nasojejunal tube
NRS	Nutrition Risk Screening
ONS	oral nutrition supplement
OS	overall survival
P2P	Pathways to Prevention
PEG	percutaneous endoscopic gastrostomy
PICOTS	population, intervention, comparator, outcome, timing and setting
PMID	PubMed Identification Number
PN	parenteral nutrition
PNI	pre-treatment nutrition intervention
POD	post-operative day
PRISMA	Preferred Items for Reporting in Systematic Reviews and Meta-Analyses
PRO	patient reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PUFA	polyunsaturated fat
QOL	quality of life
RCT	randomized controlled trial
RNA	ribonucleic acid
ROB	risk of bias
RT	radiotherapy
SF-36	short-form health survey
SIRS	systemic inflammatory response syndrome
SPN	standard parenteral nutrition

SSI	surgical site infection
TPN	total parenteral nutrition
TSF	triceps skin fold
UTD	unable to determine
WPI	whey protein isolate

Appendixes

Appendix A. Methods

Search Strategy

Search Details and Sources

The search strategy was designed and conducted by an experienced systematic review/medical librarian with input from the investigators. We applied the following limits or filters to the database searches:

- Date. We considered a literature search starting in 2000 sufficient for the purpose of this review. Date limitation was done in PICO Portal.
- Language. Publications were excluded if they were written in a language other than English. This was due to resource constraints.
- Publication status. We searched for published studies.
- Humans or organisms. A filter was used to remove animal studies.
- Study Design. The search was limited to randomized controlled trials, controlled trials, and observational cohort studies. After review of the breadth of included studies, study designs were further limited to randomized controlled trials randomizing at least 50 participants (i.e., 25 individuals per arm) to identify the literature with the highest likelihood of having statistical power to detect an effect from a nutrition intervention. The updated search on July 22, 2022 was limited to randomized controlled trials.

We conducted a comprehensive literature search in May 2021 (updated July 2022). We searched the following databases:

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 21, 2021> Date searched: May 20, 2021
- Cochrane Central Register of Controlled Trials (Wiley) Issue 4 of 12, April 2021 Date searched: May 21,2021
- Embase Classic+Embase <1947 to 2021 May 20> (Ovid) Date searched: May 20, 2021.

For the contextual question we conducted a literature search through July 2022 to more broadly understand the effectiveness of nutrition interventions from a cost-perspective, including evaluations that reported information on intervention costs as well as cost-effectivenes, cost-benefit and value analyses. We searched the following databases:

- References of relevant systematic reviews and meta analysis (line 35 of Ovid MEDLINE search strategy below)
- Web search engines/specific web sites. We searched for grey literature using Google. The first 200 Google results yielded by each search string were reviewed.
- Search of the Center for the Evaluation of Value and Risk in Health, Tufts Cost-Effectiveness Analysis Registry

Database Search Strategies

Updated Search: Ovid MEDLINE(R) ALL <1946 to July 22, 2022>

1 Nutrition Therapy/ or Diet Therapy/ or ((diet* or nutrition*) adj3 (counsel* or intervention* or support* or supplement* or therap*)).ti,ab. 1
2 Prebiotics/ or Probiotics/ or Synbiotics/ or (prebiotic* or probiotic* or symbiotic* or synbiotic*).ti,ab.
3 Enteral Nutrition/ or Nutritional Support/ or exp Parenteral Nutrition/ or ((enteral or gastrostomy or jejunostomy or oral or parenteral or tube) adj3 (feeding or nutrition*)).ti,ab.
4 Caloric Restriction/ or Diet, Reducing/ or (calori* restrict* diet* or intermittent fasting or fasting mimicking diet* or short-term fasting).ti,ab.
5 Diet, High-Protein/ or Diet, Ketogenic/ or Diet, Carbohydrate-Restricted/ or Diet, High-Protein Low-Carbohydrate/ or Diet, Mediterranean/ or (high-protein diet* or high-calorie diet* or ketogenic diet* or mediterranean diet*).ti,ab.
6 or/1-5
7 Brachytherapy/ or Chemoprevention/ or Chemoradiotherapy/ or Chemoradiotherapy, Adjuvant/ or Chemotherapy, Adjuvant/ or Consolidation Chemotherapy/ or exp Neoplasms/ or Radiotherapy/ or (cancer* or carcinoma* or chemoprevention or chemotherap* or chemoradiotherap* or leuk?emia* or melanoma* or myeloma* or neoplasm* or radiotherap* or radiation therap*).ti,ab.
8 6 and 7
9 control groups/ or double-blind method/ or placebo effect/ or random allocation/ or exp randomized controlled trial/ or single-blind method/
10 (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
11 (random* or sham or placebo*).ti,ab,hw,kf.
12 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
13 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
14 or/9-13
15 8 and 14
16 limit 15 to english language
17 limit 16 to dt=20210501-20220731

Database: Embase <1974 to 2022 Week 29>

1 ((diet* or nutrition*) adj3 (counsel* or intervention* or support* or supplement* or prebiotic* or probiotic* or symbiotic* or synbiotic* or therap*)).ti,ab. or diet therapy/ or nutritional counseling/ or diet supplementation/
2 ((enteral or gastrostomy or jejunostomy or oral or parenteral or tube) adj3 (feeding or nutrition*)).ti,ab. or nutritional support/ or parenteral nutrition/ or enteric feeding/
3 (malnutrition universal screening or malnutrition screening or nutrition* assessment or nutrition* risk screening).ti,ab.
4 (calori* restrict* diet* or intermittent fasting or fasting mimicking diet* or short-term fasting).ti,ab. or caloric restriction/ or intermittent fasting/ or exp low calorie diet/
5 (high-protein diet* or high-calorie diet* or ketogenic diet or mediterranean diet).ti,ab. or exp

ketogenic diet/ or exp protein diet/ or Mediterranean diet/ or low carbohydrate diet/
6 or/1-5
7 (cancer* or carcinoma* or chemoprevention or chemotherap* or chemoradiotherap* or leuk?emia* or melanoma* or myeloma* or neoplasm* or radiotherap* or radiation therap*).ti,ab. or exp neoplasms subdivided by anatomical site/ or cancer chemotherapy/ or chemoprophylaxis/ or consolidation chemotherapy/ or cancer radiotherapy/ or brachytherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/
8 6 and 7
9 (rats or rat or rabbit or porcine or cow or cows or chicken* or horse or horses or mice or mouse or bovine or sheep or ovine or murinae or cats or cat or dog or dogs or rodent or swine).tw.
10 8 not 9
11 exp randomized controlled trial/ or controlled clinical trial/ or control group/ or double blind procedure/ or randomization/ or single blind procedure/ or placebo effect/
12 (control* adj3 (study or studies or trial* or group*)).ti,ab,kw.
13 (random* or sham or placebo*).ti,ab,kw.
14 ((quasiexperimental or quasi experimental) adj3 (study or studies or trial*)).ti,ab,kw.
15 or/11-14
16 10 and 15
17 limit 16 to dd=20220701-20220731
18 limit 17 to conference abstracts
19 17 not 18

Cochrane Central Register of Controlled Trials Date Run: 31/07/2022
Issue 7 of 12, July 2022
25 total including 8 clinical trials from ct.gov

ID Search Hits
#1 [mh ^"diet therapy"] or [mh ^"nutrition therapy"]
#2 (diet NEAR/3 (counsel or intervention or support or supplement or therapy)):ti,ab (Word variations have been searched)
#3 (nutrition NEAR/3 (counsel or intervention or support or supplement or therapy)):ti,ab (Word variations have been searched)
#4 [mh prebiotics] or [mh probiotics] or [mh symbiotics] or [mh synbiotics]
#5 (prebiotic? or probiotic? or symbiotic? or synbiotic?):ti,ab
#6 [mh "nutritional support"] or [mh "enteral nutrition"] or [mh "parenteral nutrition"]
#7 enteral:ti,ab or gastrostomy:ti,ab or jejunostomy:ti,ab or parenteral:ti,ab or (tube near/2 feeding):ti,ab
#8 [mh "caloric restriction"] or [mh "diet, reducing"]
#9 (calorie near/3 restrict):ti,ab or (intermittent near/2 fasting):ti,ab or (fasting near/2 mimicking):ti,ab or ("short term" near/2 fasting):ti,ab (Word variations have been searched)
#10 [mh "Diet, High-Protein"] or [mh "diet, ketogenic"] or [mh "diet, carbohydrate-restricted"] or [mh "diet, high-protein low-carbohydrate"] or [mh "diet, mediterranean"]
#11 ("high protein" near/3 diet):ti,ab or ("high calorie" near/3 diet):ti,ab or (ketogenic near/3 diet):ti,ab or (Mediterranean near/3 diet):ti,ab (Word variations have been searched)
#12 [OR #1-#11]
#13 [mh Neoplasms] or [mh chemoprevention] or [mh chemoradiotherapy] or [mh

chemoradiotherapy] or [mh "chemoradiotherapy, adjuvant"] or [mh "chemotherapy, adjuvant"] or [mh "consolidation chemotherapy"] or [mh ^radiotherapy] or [mh brachytherapy]
#14 (cancer or carcinoma or chemoprevention or chemotherapy or chemoradiotherapy or leukemia or melanoma or myeloma or neoplasm or radiotherapy or "radiation therapy" or "radiation therapies"):ti,ab (Word variations have been searched)
#15 #13 or #14 235400
#16 #12 and #15 in Trials 4965
2022-05-01 to 2022-07-31: 25 total including 8 clinical trials from clinicatrials.gov

Original Searches May 2021

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to May 21, 2021>

1 Nutrition Therapy/ or diet therapy/ or ((diet* or nutrition*) adj3 (counsel* or intervention* or support* or supplement* or therap*)).ti,ab.
2 Prebiotics/ or Probiotics/ or Synbiotics/ or (prebiotic* or probiotic* or symbiotic* or synbiotic*).ti,ab.
3 Enteral Nutrition/ or Nutritional Support/ or exp Parenteral Nutrition/ or ((enteral or gastrostomy or jejunostomy or oral or parenteral or tube) adj3 (feeding or nutrition*)).ti,ab.
4 Caloric Restriction/ or Diet, Reducing/ or (calori* restrict* diet* or intermittent fasting or fasting mimicking diet* or short-term fasting).ti,ab.
5 Diet, High-Protein/ or Diet, Ketogenic/ or Diet, Carbohydrate-Restricted/ or Diet, High-Protein Low-Carbohydrate/ or Diet, Mediterranean or (high-protein diet* or high-calorie diet* or ketogenic diet* or mediterranean diet*).ti,ab. or /
6 or/1-5
7 Brachytherapy/ or Chemoprevention/ or Chemoradiotherapy/ or Chemoradiotherapy, Adjuvant/ or Chemotherapy, Adjuvant/ or Consolidation Chemotherapy/ or exp Neoplasms/ or Radiotherapy/ or (cancer* or carcinoma* or chemoprevention or chemotherap* or chemoradiotherap* or leuk?emia* or melanoma* or myeloma* or neoplasm* or radiotherap* or radiation therap*).ti,ab.
8 Controlled Clinical Trial/ or Control Groups/ or Double-Blind Method/ or Placebo Effect/ or exp Randomized Controlled Trial/ or Random Allocation/ or Single-Blind Method/
9 (control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf.
10 (random* or sham or placebo*).ti,ab,hw,kf.
11 ((quasiexperimental or quasi experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
12 (nonrandom* or non random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
13 or/8-12
14 Epidemiologic Studies/
15 exp Case-Control Studies/
16 exp Cohort Studies/
17 Cross-Sectional Studies/
18 (epidemiologic adj (study or studies)).ti,ab.
19 case control*.ab,ti.
20 (cohort adj3 (study or studies)).ti,ab.
21 cross sectional.ab,ti.

22 cohort analy*.ab,ti.
23 (follow up adj3 (study or studies)).ti,ab.
24 longitudinal.ti,ab.
25 retrospective*.ti,ab.
26 prospective*.ti,ab.
27 (observ* adj3 (study or studies)).ti,ab.
28 or/14-27
29 13 or 28
30 6 and 7 and 29
31 (rats or rat or rabbits or rabbit or porcine or cow or cows or chicken* or horse or horses or mice or mouse or bovine or sheep or ovine or murinae or cats or cat or dog or dogs or rodent or swine or pigs or pig).tw.
32 30 not 31
33 limit 32 to (comment or editorial or letter or news or newspaper article or personal narrative or preprint)
34 32 not 33
35 limit 34 to (meta analysis or "systematic review")
36 34 not 35
37 limit 36 to english language

Embase Classic+Embase <1947 to 2021 May 20> (Ovid)

1 diet therapy/ or nutritional counseling/ or ((diet* or nutrition*) adj3 (counsel* or intervention* or support* or supplement* or therap*)).ti,ab.
2 enteric feeding/ or nutritional support/ or parenteral nutrition/ or ((enteric or enteral or gastrostomy or jejunostomy or oral or parenteral or tube) adj3 (feeding or nutrition*)).ti,ab.
3 diet supplementation/ or prebiotic agent/ or probiotic agent/ or synbiotic agent/ or (prebiotic* or probiotic* or symbiotic* or synbiotic*).ti,ab.
4 exp diet restriction/ or (calori* restrict* diet* or intermittent fasting or fasting mimicking diet* or short-term fasting).ti,ab.
5 low carbohydrate diet/ or exp ketogenic diet/ or exp protein diet/ or Mediterranean diet/ or (high-protein diet* or high-calorie diet* or ketogenic diet or mediterranean diet).ti,ab.
6 1 or 2 or 4 or 5
7 adjuvant chemoradiotherapy/ or brachytherapy/ or cancer chemotherapy/ or cancer radiotherapy/ or chemoprophylaxis/ or chemoradiotherapy/ or consolidation chemotherapy/ or exp malignant neoplasms/ or (cancer* or carcinoma* or chemoprevention or chemotherap* or chemoradiotherap* or leuk?emia* or melanoma* or myeloma* or neoplasm* or radiotherap* or radiation therap* or tumo?r*).ti,ab.
8 6 and 7
9 (rats or rat or rabbits or rabbit or porcine or cow or cows or chicken* or horse or horses or mice or mouse or bovine or sheep or ovine or murinae or cats or cat or dog or dogs or rodent or swine or pig or pigs).tw.
10 8 not 9
11 controlled clinical trial/ or control group/ or double blind procedure/ or placebo effect/ or exp randomized controlled trial/ or randomization/ or single blind procedure/
12 (control* adj3 (group* or study or studies or trial*)).ti,ab,kw.

13 (placebo or random* or sham).ti,ab,kw.
14 ((quasiexperimental or quasi experimental) adj3 (study or studies or trial*)).ti,ab,kw.
15 or/11-14
16 10 and 15
17 epidemiology/ or epidemiolog* study.ti,ab.
18 cross-sectional study/ or cross sectional.ti,ab,kw.
19 cohort analysis/
20 case control study/
21 observational study/
22 prospective study/
23 longitudinal study/
24 retrospective study/
25 case control*.ti,ab,kw.
26 (cohort adj3 (study or studies)).ti,ab,kw.
27 cross sectional.ti,ab,kw.
28 cohort analy*.ti,ab,kw.
29 (longitudinal or prospective* or retrospective*).ti,ab,kw.
30 (observ* adj3 (study or studies)).ti,ab,kw.
31 or/17-30
32 15 or 31
33 10 and 33
34 limit 34 to english language
35 limit 34 to (conference abstract or conference paper or "conference review" or editorial or letter or note or "review")
36 34 not 35
37 limit 36 to (meta analysis or "systematic review")
38 36 not 37

Cochrane Central Register of Controlled Trials (Wiley)
Issue 5 of 12, May 2021

ID Search Hits
#1 [mh ^"diet therapy"] or [mh ^"nutrition therapy"]
#2 (diet* NEAR/3 (counsel* or intervention* or support* or supplement* or therap*)):ti,ab
#3 (nutrition* NEAR/3 (counsel* or intervention* or support* or supplement* or therap*)):ti,ab
#4 [mh prebiotics] or [mh probiotics] or [mh symbiotics] or [mh synbiotics]
#5 (prebiotic* or probiotic* or symbiotic* or synbiotic*):ti,ab
#6 [mh "nutritional support"] or [mh "enteral nutrition"] or [mh "parenteral nutrition"]
#7 (enteral or gastrostomy or jejunostomy or parenteral or tube feeding):ti,ab
#8 [mh "caloric restriction"] or [mh "diet, reducing"]
#9 (calori* NEAR restrict* or intermittent NEAR fasting or fasting NEAR mimicking or short-term NEAR fasting):ti,ab
#10 [mh "Diet, High-Protein"] or [mh "diet, ketogenic"] or [mh "diet, carbohydrate-restricted"] or [mh "diet, high-protein low-carbohydrate"] or [mh "diet, mediterranean"]
#11 (high-protein diet* or high-calorie diet* or ketogenic diet or mediterranean diet):ti,ab
#12 [OR #1-#11]

#13 [mh brachytherapy] or [mh chemoprevention] or [mh chemoradiotherapy] or [mh chemoradiotherapy] or [mh "chemoradiotherapy, adjuvant"] or [mh "chemotherapy, adjuvant"] or [mh "consolidation chemotherapy"] or [mh Neoplasms] or [mh ^radiotherapy]
#14 (cancer* or carcinoma* or chemoprevention or chemotherap* or chemoradiotherap* or leuk?emia* or melanoma* or myeloma* or neoplasm* or radiotherap* or radiation therap*):ti,ab
#15 #13 or #14
#16 #12 and #15 3647 (PubMed, Embase, CINAHL)

Tufts CEA Registry Search Terms

“diet therapy" or “nutrition therapy" or “counsel*” or “nutrition supplement*” or “enteral nutrition” or “parenteral nutrition” or “oral nutrition supplement” or “caloric restriction” or “diet” AND “cancer” or “carcinoma”

Risk of Bias Assessment Guide

INSTRUCTIONS: Review the methods of each trial and assess each risk of bias component as described in these instructions. You may need to have separate assessments for different outcomes (i.e., different measures; different time points may have different attrition rates).

Table A.1. Selection bias

Description/Guiding Questions	Notes
Systematic differences between baseline characteristics of the groups that arise from self-selection of treatments, physician-directed selection of treatments, or association of treatment assignments with demographic, clinical, or social characteristics. • Did method of randomization create biased allocation to interventions (inadequate randomization)?	• "Good" Randomization: Detailed methodology would include providing method of randomization such as use of a random numbers table, or computer random number generator. Limited methodology would be the study saying simply saying they randomized in the methods or provided limited detail such as randomizing by a 2:1 ratio. • "Poor"/No Randomization: Randomized based on week of the month of birthday or a non-randomized clinical trial, observational study.

Figure A.1. Selection bias assessment guidance

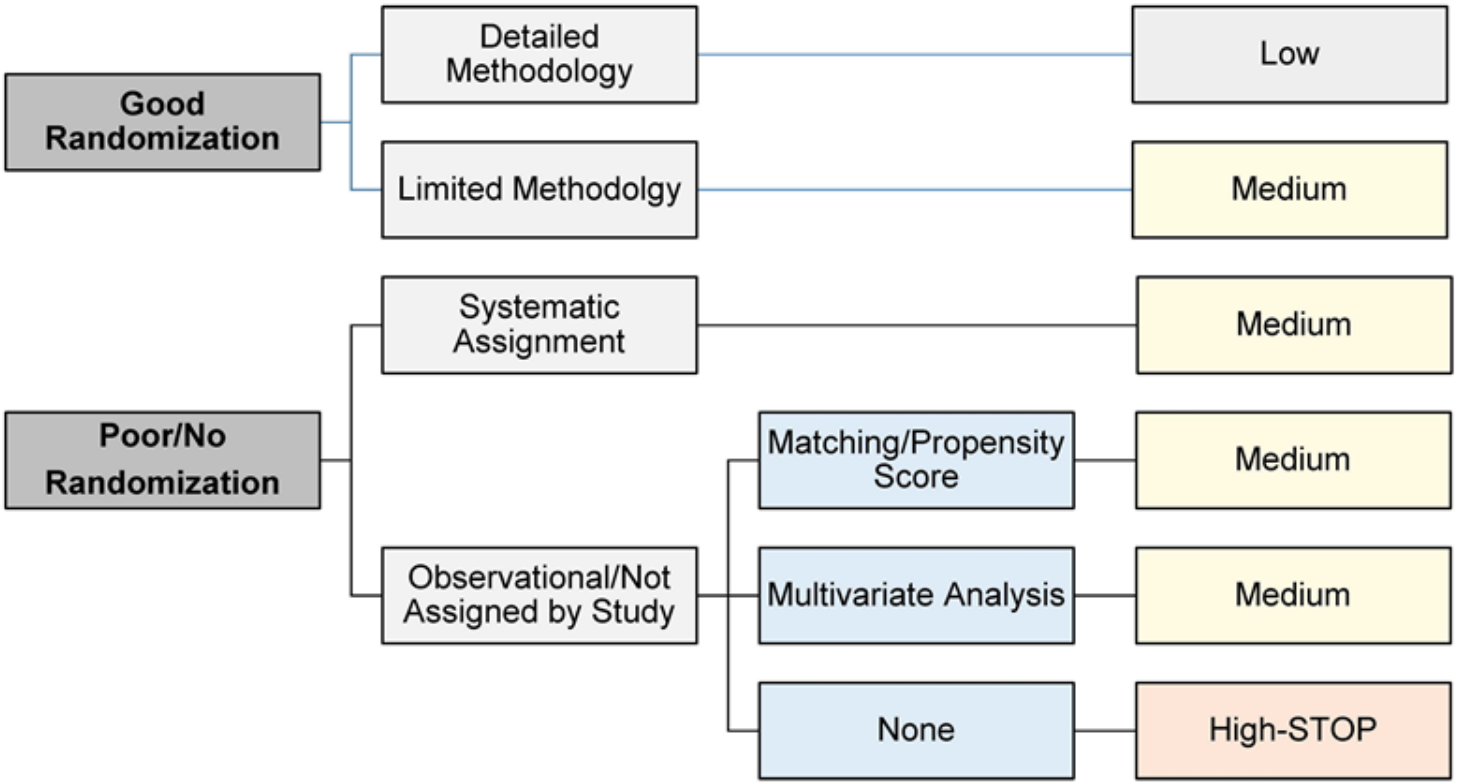


Table A.2. Detection bias

Description/Guiding Questions	Notes
Systematic differences in outcomes assessment among groups being compared, including systematic misclassification of the exposure or intervention, covariates, or outcomes because of variable definitions and timings, diagnostic thresholds, recall from memory, inadequate assessor blinding, and faulty measurement techniques. Erroneous statistical analysis might also affect the validity of effect estimates. • Were the outcome assessors blinded to the intervention ("outcome assessor blinded")? • Was the timing of the outcome assessment similar in all groups ("comparable timing outcomes assessment")? • Was the scale used to measure outcomes validated, reliable? • Were outcomes measured in clinically meaningful ways?	• Independent assessor is someone not directly involved in delivering the intervention

Figure A.2. Detection bias assessment guidance

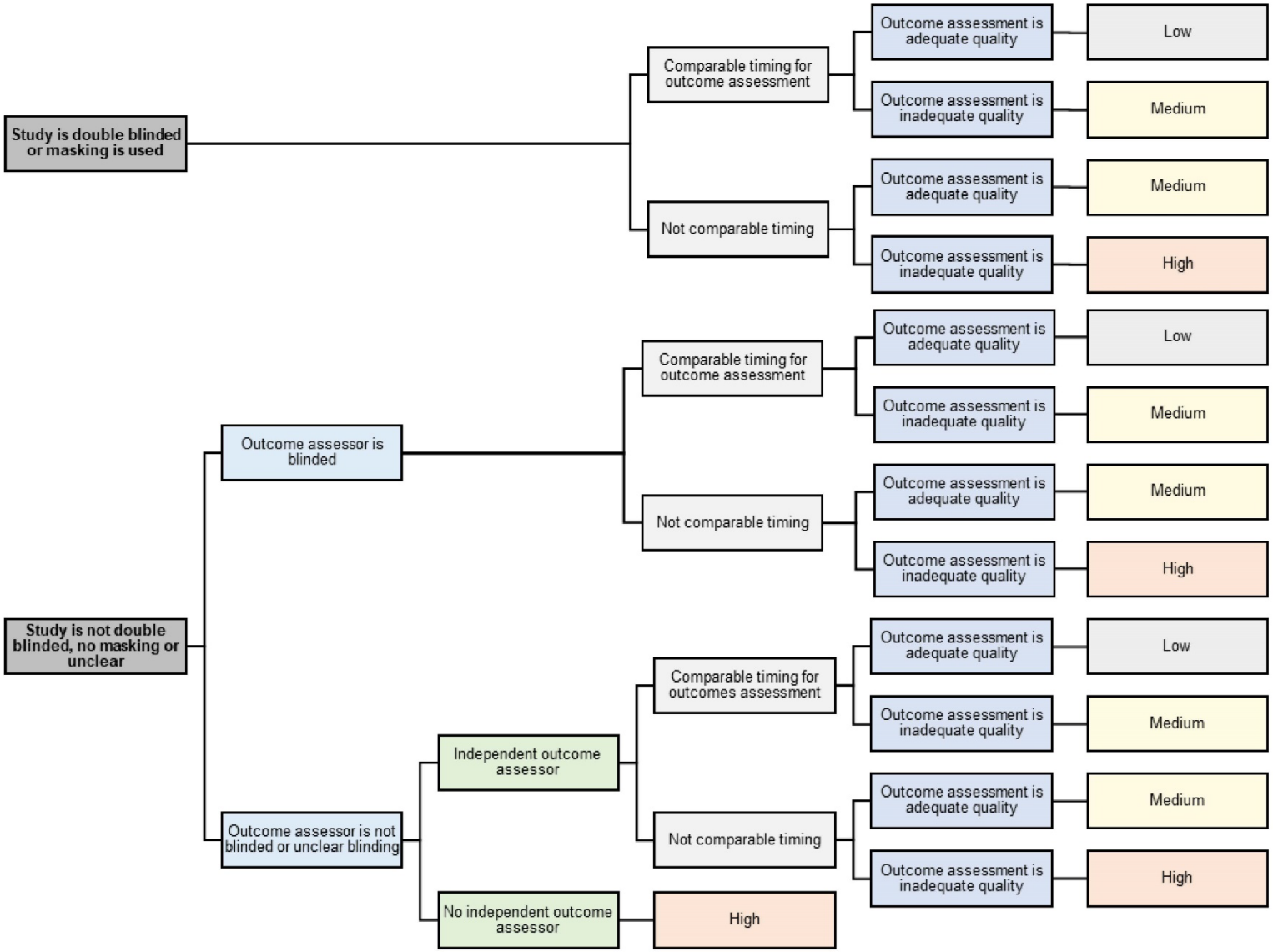
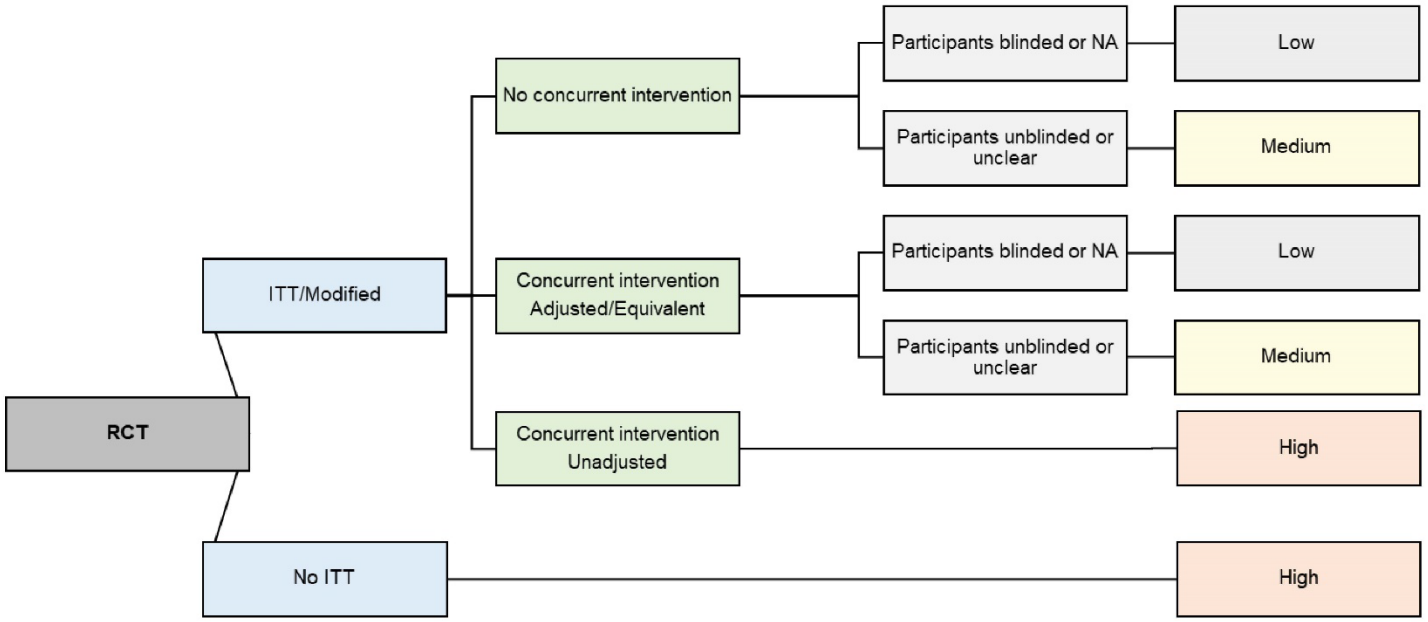


Table A.3. Performance bias

Description/Guiding Questions	Notes
Systematic differences in the care provided to participants and protocol deviation. Examples include contamination of the control group with the exposure or intervention, problems with fidelity to the intervention, unbalanced provision of additional interventions or co-interventions, difference in co-interventions, and inadequate blinding of providers and participants.	• Intention-to-Treat (ITT): Includes every subject according to randomized treatment assignment. Ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. Concurrent Intervention: Study participants are receiving another intervention (i.e., treatment) that is not part of the intervention being tested. Example: Participants are randomized to a physical activity intervention (or no intervention), but are also dieting. If the denominator at baseline and in the results are reported and both numbers match, we can assume ITT unless there is an explicit statement in the methods for another approach.

Figure A.3. Performance bias assessment guidance



Abbreviations: ITT=intention to treat; NA= not applicable; RCT=randomized controlled trial.

Table A.4. Fidelity to intervention

Description/Guiding Questions	Notes
We anticipate that care delivery studies will generally fall in the range of NIH Stage 3 to 4, with the possibility that one or a few may be carried out as quality improvement and thus Stage 5. Since the Stage Model is explicitly designed to balance, or trade off, internal and external validity, we will approach risk of bias assessment as a threshold requirement rather than a continuum. • Look for reporting on intervention compliance, any data reported on consistency of intervention use, or any mechanisms used to ensure compliance (e.g., reminders, guides, manuals).	• Information may appear in methods, results, or discussion sections.

Table A.5. Fidelity to intervention assessment guidance

Domain	Options	Rating
Fidelity to intervention	Yes (at least 70%)	Low
	Yes-adaptation planned/ replicable	Medium
	No-adaptation not planned	High
	Unclear/Not Reported	Medium

Table A.6. REPORTING Bias

Description/Guiding Questions	Notes
Systematic differences between reported and unreported findings (e.g., differential reporting of outcomes or harms, incomplete reporting of study findings, potential for bias in reporting through source of funding). • Was a select group of outcomes reported?	• Compare results to methods section and/ or protocol. • Check if some results are reported in a different publication.

Table A.7. Reporting bias assessment guidance

Domain	Options	Rating
All outcomes reported	Yes	Low
	No	Medium
	Not Reported	Medium

Table A.8. Attrition bias

Description/Guiding Questions	Notes
Systematic differences in the loss of participants from the study and how they were accounted for in the results (e.g., incomplete follow-up, differential attrition). Those who drop out of the study or who are lost to follow-up may be systematically different from those who remain in the study. Attrition bias can potentially change the collective (group) characteristics of the relevant groups and their observed outcomes in ways that affect study results by confounding and spurious associations. • Reasons for incomplete/missing data adequately explained? • Do the author's attempt to address attrition in the analysis?	• Attrition assessment is dependent on overall study duration (see flowchart) Report attrition rate in spreadsheet. If a study reports outcomes at multiple intervals (e.g., 6 months, 12 months, 18 months) assess attrition at the first relevant time point and the last time-point separately, you do not need to do every time point. Analysis should be done with appropriate method (i.e. sensitivity analysis with various scenarios); last value forward would only be appropriate for interventions that are supposed to improve the outcomes (i.e. memory training that intends to improve memory). Look for withdrawals in the flow diagram that are not accounted for in results table.

Figure A.4. Attrition bias assessment guidance

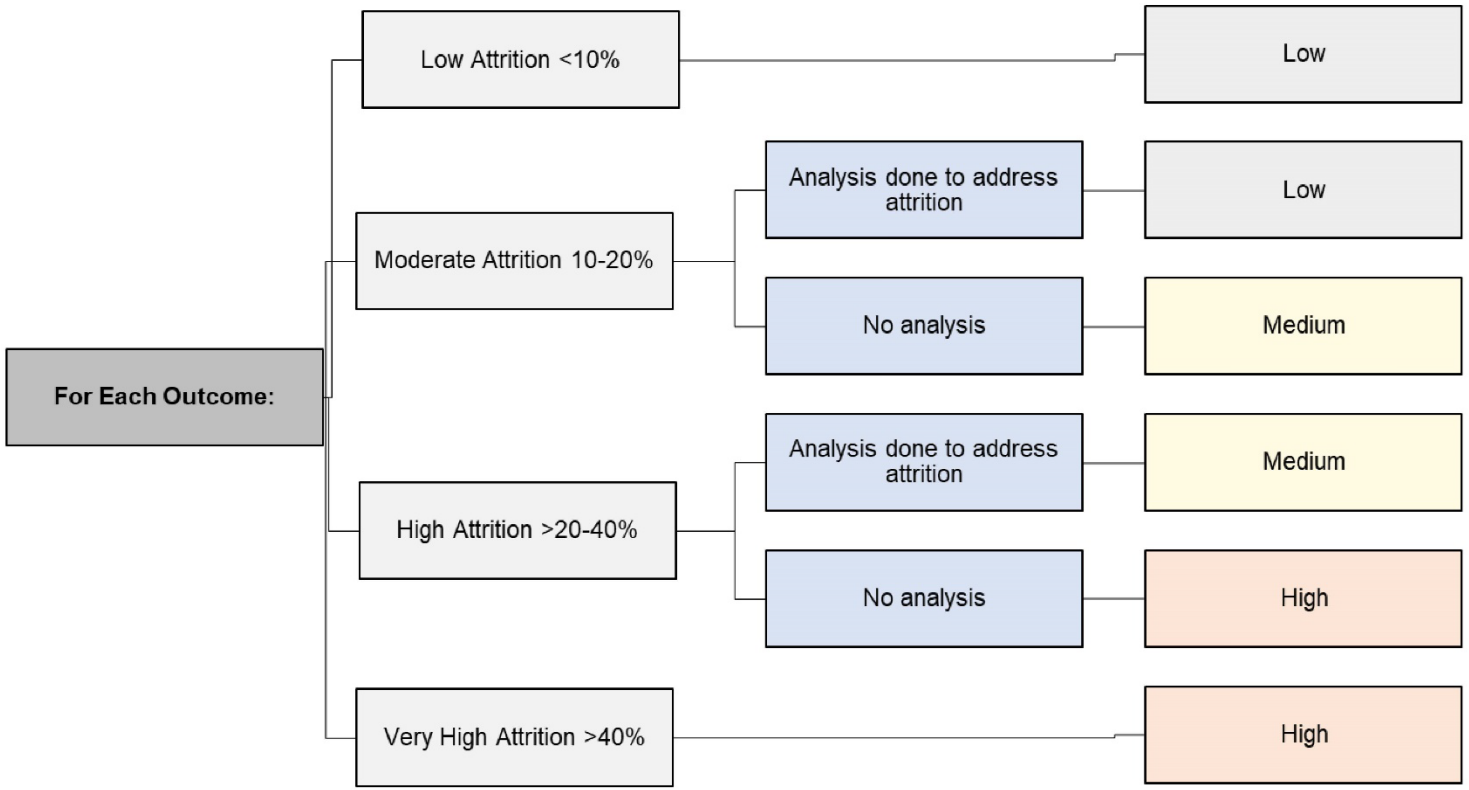
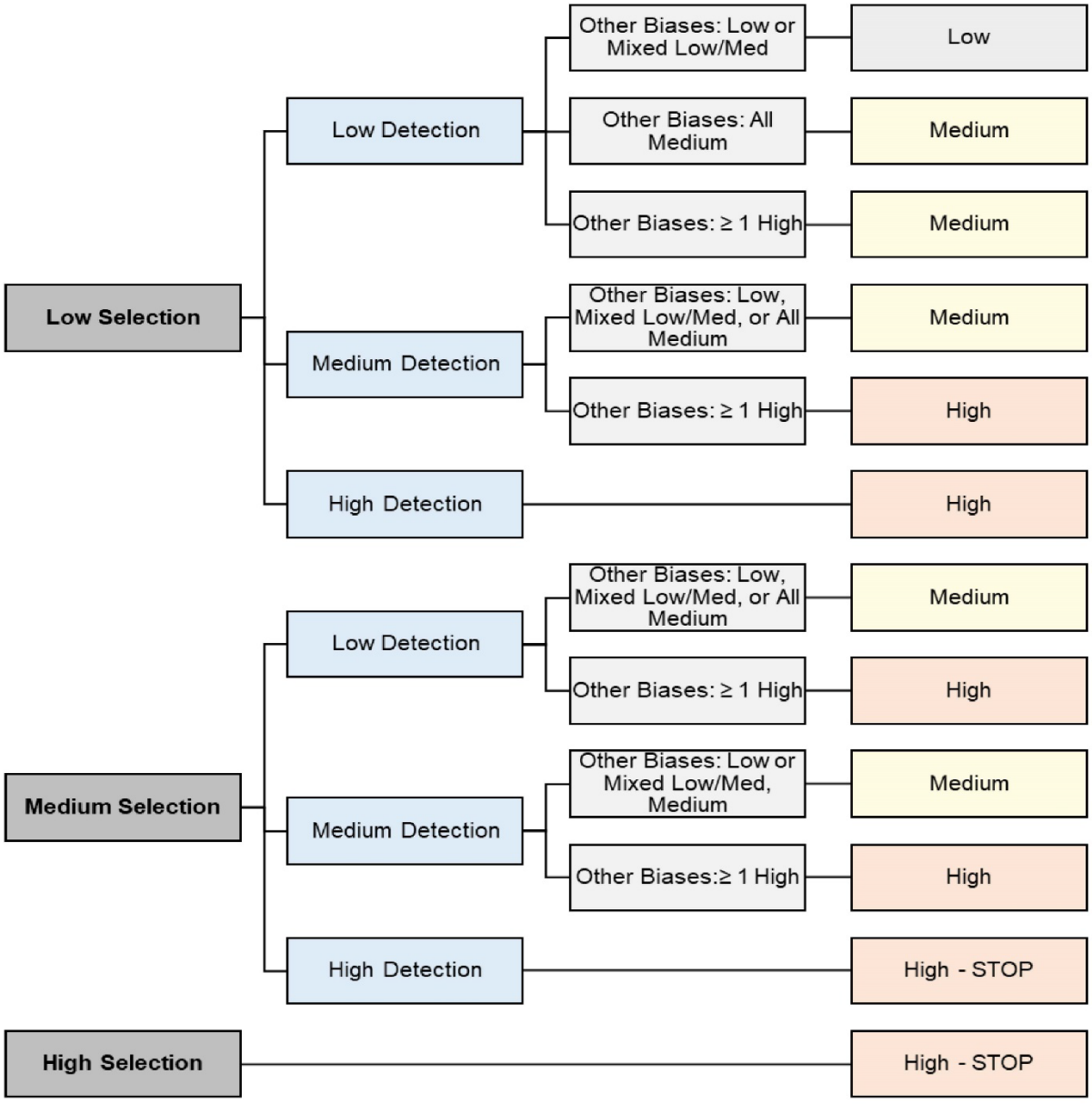


Figure A.5. Overall risk of bias assessment guidance



Appendix B. Studies Excluded at Full Text

P=Population
I=Intervention
C=Comparison
O=Outcome
S=Study Design
SS=Sample Size
PT=Publication Type
NE=Non English
D=Duplicate
OR=Other Reason
R=Retracted

1. Clinical Efficacy of FOLFOX Chemotherapy Combined with Nutritional Support in the Treatment of Gastrointestinal Malignancies. Anti-tumor pharmacy. 2018;8(4):635-8 and 52. doi: 10.3969/j.issn.2095-1264.2018.04.35. PMID: CN-01966940. PT
2. Effect of postoperative diet nursing with patient involved on nutritional status of the patients with rectal cancer. Chinese journal of clinical nutrition. 2018;26(5):288-92. doi: 10.3760/cma.j.issn.1674-635X.2018.05.006. PMID: CN-01993733. PT
3. The Effect of n-3 polyunsaturated fatty acid supplementation on the nutritional condition of the patients and on the achievement of the chemotherapy against advanced colorectal cancer. Therapeutic research. 2019;40(8):649-60. PMID: CN-02092344. PT
4. Effect of nutrition intake method with adaptive viscosity on nutritional status of laryngeal cancer patients with dysphagia after surgery and radiotherapy. Chinese journal of clinical nutrition. 2019;27(2):113-7. doi: 10.3760/cma.j.issn.1674-635X.2019.02.009. PMID: CN-02003689. PT
5. Effect of Targeted Nutritional Intervention on Intestinal Flora, Defecation Function, and Postoperative Complications in Patients Who Underwent Radical Resection of Rectal Carcinoma. Anti-tumor pharmacy. 2019;9(2):338-43. doi: 10.3969/j.issn.2095-1264.2019.02.34. PMID: CN-01993849. PT
6. Effects of oral nutritional supplements on body weight and life qualityin post-discharge patients with gastricor colorectal cancer: a prospective randomized controlled clinical trial. Chinese journal of clinical nutrition. 2019;27(5):271-5. doi: 10.3760/cma.j.issn.1674-635X.2019.05.002. PMID: CN-02147061. PT
7. Effects of whole- course MDT nutrition management on radiotherapy in elderly patients with esophageal cancer. Chinese journal of clinical oncology. 2020;47(1):29-33. doi: 10.3969/j.issn.1000-8179.2020.01.461. PMID: CN-02199723. PT
8. Aarts MA, Okrainec A, Glicksman A, et al. Adoption of enhanced recovery after surgery (ERAS) strategies for colorectal surgery at academic teaching hospitals and impact on total length of hospital stay. Surgical Endoscopy. 2012;26(2):442-50. doi: 10.1007/s00464-011-1897-5. PMID: 51677040. I
9. Abdelgadir MA, Mahadi SE, Nasr AO, et al. Role of jejunostomy feeding catheter as a model for nutritional support. International Journal Of Surgery. 2010;8(6):439-43. doi: 10.1016/j.ijsu.2010.05.006. PMID: 20538080. C
10. Abdellatif AA, Shams MMK, Helmy AFH. A comparative Study between Tube Feeding versus Parenteral Nutrition in GIT Cancer Patients in ICU. QJM : monthly journal of the Association of Physicians. 2021;114(S). doi: 10.1093/qjmed/hcab086.002. PMID: CN-02346319. PT
11. Abe T, Hosoi T, Kawai R, et al. Perioperative enteral supplementation with glutamine, fiber, and oligosaccharide reduces early postoperative surgical stress following esophagectomy for esophageal cancer. Esophagus. 2019;16(1):63-70. doi: 10.1007/s10388-018-0630-z. PMID: 30030739. S
12. Achiam MP, Nilsson M, Åkesson O, et al. Perioperative Strategies in Esophageal Cancer Resection in 12 Nordic University Hospitals [abstract]. Diseases of the Esophagus. 2022;35(Supplement_1):10-. doi: 10.1093/dote/doac015.104. PMID: CN-02421964. PT

13. Achilli P, Mazzola M, Bertoglio CL, et al. Preoperative immunonutrition in frail patients with colorectal cancer: an intervention to improve postoperative outcomes. International Journal of Colorectal Disease. 2020;35(1):19-27. doi: 10.1007/s00384-019-03438-4. PMID: 31754818. S

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Appendix C. Evidence Tables for Chapter 5

Dietary Supplements

Table C.1. Characteristics of included studies: dietary supplements prior to cancer treatment (KQ1)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Dominant Cancer Treatment Type Limited to Malnourished Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Dechaphunkul, 2022[1] (35007812) Asia Key Question 1, 3 Not conducted	110 52 years 21% female Race NR	Head & Neck 76% Stage IV Chemotherapy No Other (Nutritional Risk Index)	Immunonutrition with FA's, arginine, fiber & nucleotides, 3x/day for 5 days before each chemotherapy session. Outpatient Nutritionist Oral	Standard enteral formula, 3x/day for 5 days before each chemotherapy	Weight or body composition changes Symptoms Survival
de Miranda Torrinhas, 2013[2] (23398953) Other Key Question 1 High	63 58 years 37% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other metric	Supplements (fish oil-based lipid emulsions) Inpatient Other Provider Parenteral	Lipid emulsion rich in medium-chain triglycerides	Adverse events Length of stay
Feijo, 2019[3] (30710885) Other Key Question 1 High	68 58 years 35% female Race NR	Gastrointestinal 7% Stage IV disease Chemotherapy alone No Multiple tools	Single Supplement (received supplementation of formula enriched with omega-3 fractionated in 2 steps of 200 mL/d each) Outpatient Dietitian/nutritionist Oral	Received standard supplementation without omega-3	Weight or body composition changes

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Dominant Cancer Treatment Type Limited to Malnourished Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Kaya, 2016[4] (26782276) Europe Key Question 1 Not conducted	58 58 years 6% female Race NR	Other % Stage IV disease NR Surgery alone No Screening tool NR	Supplements (immune modulating formulae (enriched with arginine, omega-3 fatty acids and nucleotides) for ten days preoperatively) Setting NR Provider NR Route of Intervention NR	Normal diet without any additional nutritional product	Changes in nutritional status
Lende, 2019[5] (31703648) Europe Key Question 1 Not conducted	80 Age NR 100% female Race NR	Other 0% Stage IV disease Surgery alone No Screening tool NR	Supplements (400 ml Nutrica preop (12% CHO, 2% glucose, 10% polysaccharides) 18 hr before breast cancer surgery) Inpatient Physician Oral	Standard fasting preoperative protocol with unlimited access to drinking water	Adverse events Survival

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; CHO = carbohydrate.
*For select studies only.
†Reports median age when mean is not available.

Nutrition Support Including Oral Nutrition Supplements

Table C.2. Characteristics of included studies: use of nutrition support including oral nutrition supplements prior to cancer treatment (KQ1)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Burden, 2017[6] (28052576) Europe Key Question 1 Medium	101 70 years 33% female Race NR	Gastrointestinal 23% Stage IV disease Surgery alone Yes Other tool	Nutrition (Oral supplementation (Fortisip Compact) at a dose of 250 mL daily a minimum of 5 days pre-operatively) Multiple settings Dietitian/nutritionist Oral	The control group received the same leaflet and therapy with nutritionist and boxes the same size/weight but filled with water	Weight or body composition changes Changes in nutritional status Adverse events Survival Length of stay
Burden, 2011[7] (21699587) Europe Key Question 1 Medium	125 65 years 38% female	Gastrointestinal 5% Stage IV disease Surgery alone No Other tool	Nutrition (400 mL of an oral supplementary drink daily and dietary advice) Inpatient Dietitian/nutritionist Oral	Received dietary advice only	Adverse events
Chen X, 2021 (33752148)[8] Asia Key Question 1,3 Medium	139 59 years 38% female Race NR	Gastrointestinal 0 Stage IV Surgery (post-chemo-radiotherapy) No Screening Tool NR	Oral Nutrition (1000 ml of 10% glucose solution 10 hr. before surgery + 500 ml of same 2-3 hr. before surgery) Setting NR Provider NR Oral	500 ml of 10% glucose solution 2-3 hr. before surgery	Adverse events Length of stay Readmissions or Emergency room visits Symptoms
Hamamoto, 2018[9] (29915986) Asia Key Question 1 High	64 70 years 48% female Race NR	Gastrointestinal 5% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (Carbohydrate-rich beverage night before surgery and before anesthesia) Inpatient Provider NR Oral	Clear drinking water 2 h prior to anesthesia	Weight or body composition changes Adverse events Length of stay

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
He F, 2022[10] (35406085) Asia Key Question 1, 3 Low	67 62 years 29% female Race/ethnicity NR	Gastrointestinal Stage NR Surgery No NRS-2002	Preoperative ONS 500 ml. x 7 days (plus NJ feedings day 1-5 post-surgery) Outpatient Dietitian Oral	Preoperative dietary advice (plus NJ feedings day 1-5 post-surgery)	Adverse events Readmissions or emergency room visits Symptoms
Kabata, 2015[11] (25091056) Europe Key Question 1 High	102 64 years 49% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other metric	Nutrition (oral nutrition supplement (Nutridrink) 14 days pre-operatively) Outpatient Provider NR Oral	Regular diet	Weight or body Composition changes Adverse events
Kruger, 2016[12] (27861546) Europe Key Question 1, 3 High	100 64 years 57% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No NRS-2002	Nutrition (in-hospital peripheral intravenous nutrition on fasting days (1000 ml peripheral intravenous nutrition, 700 kcal)) Inpatient Multiple providers Parenteral	1000 ml isotonic electrolyte solution	Weight or body composition changes Quality of life
Lee, 2021[13] (34353994) Asia Key Question 1 Medium	161 65.3 years 34% female Race NR	Gastrointestinal 7% Stage IV disease Surgery alone No Other tool	Nutrition (400 mL/day of immunonutrient-enriched ONS (Newcare Omega®), which contained high protein levels, arginine, and ω-3 fatty acids, in addition to the normal diet for 7 consecutive days prior to surgery) Inpatient Provider NR Oral	Patients in the control group had a normal diet without taking placebo.	Weight or body composition changes Adverse events Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Martin, 2017[14] (28162818) North America Key Question 1 High	71 61 years 55% female Non-Hispanic White	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Nutrition (Preoperative immunonutrition three containers a day five days prior to surgery) Inpatient Provider NR Oral	No supplemental preoperative nutrition	Changes in nutritional Status Adverse events Length of stay
Rizvanovic, 2019[15] (31309323) Europe Key Question 1, 3 Low	50 61 years 46% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No NRS-2002	Nutrition (400 mL of carb drink 22 h before surgery and 200 mL 2 h before anaesthesia) Inpatient Provider NR Oral	Fasted for 8 hours before surgery	Length of stay Quality of life Symptoms
Shen Y, 2022[16] (35307727) Asia Key Question 1 High	160 66 years 23% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening Tool NR	Nutrition (oral enteral nutrition for the three days prior to surgery along with bifidobacteria capsules 3x/day) Inpatient Provider NR Oral	Standard intestinal preparation	Adverse events Length of Stay
Tesar, 2022[17] (35258042) Europe Key Question 1, 3 Medium	120 65 years 34% female Race NR	Gastrointestinal 0% Stage IV Surgery No NRS-2002	ONS (oral nutritional supplements 2x a day for 7 days before surgery) Inpatient Provider NR Oral	No oral nutritional supplement	Weight or body composition changes Adverse events Length of Stay Functional status
Wang, 2015[18] (26125807) Asia Key Question 1 High	200 Age NR 35% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (preoperative enteral nutrition starting 1 week before surgery) Inpatient Provider NR Enteral	EN starting early after surgery	Changes in nutritional status Adverse events

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Xu, 2006[19] (16830214) Asia Key Question 1 Medium	60 59 years 40% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition (Enteral Impact® for 7 days preoperatively) Inpatient Provider NR Enteral	Conventional diet preoperatively	Adverse events Length of stay
Zhao, 2018[20] (30273016) Asia Key Question 1 High	66 62 years 14% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No NRS-2002	Nutrition (500 ml oral nutrition support (Nutrison Fiber) seven days preoperatively) Other Provider NR Oral	Routine preop diet	Weight or body Composition changes Changes in nutritional status Length of Stay

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NRS = nutrition risk screening; EN = enteral nutrition;
*For select studies only.
†Reports median age when mean is not available.

Risk of Bias and Outcomes Assessment

Table C.3. Risk of bias assessment: use of dietary supplements prior to cancer treatment (KQ1)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
de Miranda Torrinhas, 2013[2] (23398953)	Inpatient	Low	Low	High	Medium	Low	High (25%)	High
Feijo, 2019[3] (30710885)	30 days	Low	Medium	High	Medium	Low	Medium (18%)	High

Abbreviations: PMID = PubMed Identification Number; KQ = Key Question

Table C.4.1. Risk of bias assessment: use of nutrition support including oral nutrition supplements prior to cancer treatment (KQ1)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Burden, 2017[66] (28052576)	30 d	Medium	Medium	Medium	Medium	Low	Low (9%)	Medium
Burden, 2011[7] (21699587)	Inpatient, 30 d	Low	Medium	Medium	Low	Low	Low (7%)	Medium
Chen X, 2021[8] (33752148)	Inpatient, 30 d	Low	Medium	Medium	Medium (NR)	Low	Low (2%)	Medium
Hamamoto, 2018[99] (29915986)	X	Medium	High	X	X	X	X	High
He F 2022[10] (35406085)	Inpatient, 30 d	Low	Low	Medium	Medium (NR)	Low	Low (2%)	Low
Kabata, 2015[11] (25091056)	30 days	Low	High	High	X	X	X	High
Kruger, 2016[12] (27861546)	X	Medium	High	X	X	X	X	High
Lee, 2021[13] (34353994)	30 days post-surgery	Low	Low	High	Medium	Low	Low (9%)	Medium
Martin, 2017[14] (28162818)	X	High	X	X	X	X	X	High
Rizvanovic, 2019[15] (31309323)	POD 2	Low	Low	Medium	Medium	Low	Low (0)	Low
Shen Y, 2022[16] (35307727)	Inpatient	Low	Medium	High	Medium	Low	Low (0%)	High
Tesar 2022[17] (35258042)	Inpatient, 30d	Medium	Medium	Medium	Medium	Low	Low (2%)	Medium
Wang, 2015[18] (26125807)	X	Medium	High	X	X	X	X	High
Xu, 2006[19] (16830214)	Inpatient	Medium	Medium	Medium	Medium	Low	Low (0)	Medium
Zhao, 2018[20] (30273016)	Inpatient	Low	Medium	High	X	X	X	High

Note: X indicates domain not assessed due to already determined high risk of bias.
Abbreviations: PMID = PubMed Identification; Number; d = days; KQ= Key Question

Table C.4.2. Outcomes assessment: use of nutrition support including oral nutrition supplements prior to cancer treatment (KQ1)

Author, Year, PMID, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions / Emergency Room Visits	Survival	LOS	Treat. Tolerance	QOL	Symptoms	Functional Status
Burden, 2017[66] (28052576) Medium 30 d	101	Oral supplementation with dietary advice	Same dietary leaflet and therapy with nutritionist and boxes the same	↑weight loss	↔	↑surgical site infections ↔chest infections ↔complications	NA	↔	↔	NA	-	-	-
Burden, 2011[7] (21699587) Medium Inpatient, 30 d	125	Oral supplementary drink daily and dietary advice	Received dietary advice only	NA	NA	↔complications	NA	NA	NA	-	-	-	-
Chen X, 2021[8] (33752148) Medium Inpatient, 30 d	139	Double-dose oral CHO drink before gastrectomy	Single-dose oral CHO drink before gastrectomy	NA	NA	↔	↔ readmission ↔ reoperation	NA	↔	-	-	-	-
He F, 2022[10] (35406085) Low Inpatient, 30 d	67	Preoperative ONS 500 ml. x 7 days	Dietary advice	NA	NA	↔	↔ readmission	NA	NA	-	-	-	-

Author, Year, PMID, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions / Emergency Room Visits	Survival	LOS	Treat. Tolerance	QOL	Symptoms	Functional Status
Lee, 2021[13] (34353994) Medium 30 days post-surgery	161	Oral nutrition supplement for 7 consecutive days prior to surgery	Normal diet without taking placebo	↔weight/body composition changes ↑weight recovery after discharge	NA	↔infectious and total complications	NA	NA	↔	-	-	-	-
Rizvanovic, 2019[151515] (31309323) Low POD 2	50	Preop. Oral CHO supplement	Preop. Fasting	NA	NA	NA	NA	NA	↑	-	-	-	-
Tesar, 2022[17] (35258042) Medium Inpatient, 30d	120	oral nutritional supplements 2x a day for 7 days before surgery	No oral nutrition supplement	↔ muscle, water or fat weight	NA	↔ Clavien-Dindo complications	NA	NA	↔ ICU, hospital stay	-	-	-	-
Xu, 2006[191919] (16830214) Medium	60	Enteral Impact® for 7 days preoperatively	Conventional diet preoperatively	NA	NA	↑noninfectious complications	NA	NA	↑	-	-	-	-

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; CHO=carbohydrate; NA=not assessed

-: not applicable

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer Aes, shorter LOS than comparison group)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more Aes, longer LOS)

↔: No statistically significant difference between groups

Appendix D. Evidence Tables for Chapter 6

Dietary Supplements

Table D.1. Characteristics of included studies: use of dietary supplements prior to and during cancer treatment (spans KQ 1 and 2)

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Celik, 2009[21] (19761135) Europe Key Question 1 & 2 Not conducted	50 63 years 100% female Race NR	Other % Stage IV disease NR Surgery alone No Other tool	Supplements (immune-enhancing enteral nutrition) Inpatient Provider NR Oral	Standard, oral enteral nutrition formula	Adverse events Survival Length of stay
Cereda, 2019[22] (31568698) Europe Key Question 1 & 2, 3 Not conducted	166 65 years 40% female Race NR	Multiple cancers 81% Stage IV disease Chemotherapy alone Yes Other metric	Single Supplement (WPI supplementation) Outpatient Dietitian/nutritionist Oral	Nutritional counseling alone	Weight or body composition changes Treatment tolerance Quality of life
Ghosh, 2012[23] PMID NA Europe Key Question 1 & 2 Not conducted	60 61 years 12% female Race NR	Head & Neck 30% Stage IV disease Surgery alone No Screening Tool NR	Supplements (IMPACT ONS – added arginine, nucleotides, & omega-3-FAs) Inpatient Other Enteral	ONS with same calories & nitrogen (no supplements) same dose, timing & duration	Adverse events Survival Length of stay
Haidari, 2020[24] (32219761) Asia Key Question 1 & 2 High	81 58 years 43% female Race NR	Gastrointestinal 0% Stage IV disease Chemotherapy alone No Screening Tool NR	Supplements (added omega-3-FAs) Outpatient Provider NR Oral	Placebo capsule for omega-3 fatty acids twice/day plus a placebo vitamin D once/week started 1 week before first chemotherapy appt and going for 8 weeks	Weight or body composition changes

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Healy, 2017[25] (28742713) Europe Key Question 1 & 2 High	268 62 years % female NR Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other Tool	Single Supplement (Prosure ONS) Multiple settings Multiple providers Enteral	Standard ONS (Ensure Plus)	Weight or body composition changes Changes in nutritional status Adverse events
Jantharapattana, 2020[26] (31647147) Asia Key Question 1 & 2 Not conducted	65 57 years 18% female Race NR	Head & Neck 0% Stage IV disease Surgery alone Yes MST	Supplement (Ensure like product – Prosure) Setting NR Provider NR Oral	Conventional isocaloric supplement (Blendera)	Weight or body composition changes Adverse events
Jo, 2006[27] (16927064) Asia Key Question 1 & 2 Medium	60 57 years 52% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Single Supplement (added glutamine) Inpatient Provider NR Parenteral	TPN amino acid solution (1.3 g/kg/day amino acids) – Preop day 2-5 and postop day (not incl operation day; 7 days total)	Weight or body composition changes Adverse events Survival Length of stay
Oguz, 2007[28] (17573745) Other Key Question 1 & 2 High	109 54 years 35% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Single Supplement (added glutamine) Inpatient Multiple providers Enteral	Ensure oral (1000 ml/d x 5d preop, 500 ml/day x 2d postop then 1000ml/d 3+ more days postop)	Changes in nutritional status Adverse events Survival
Ryan, 2009[29] (19247018) Europe Key Question 1 & 2 High	53 64 years 9% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other Tool	Single Supplements (added triglycerides/fatty acids) Setting NR Dietitian/nutritionist Enteral	Iso-caloric iso-nitrogenous standard nutritional feed	Weight or body Composition changes Adverse events Survival
Serrano, 2022[30] (35606184) Canada Key Question 1 & 2, 3 Medium	71 65 years 41% female Race NR	Gastrointestinal 69% Stage IV disease Surgery No MUST	Supplements (protein supplementation rich in arginine and omega-6 and carbohydrate loading) Other Nurse Oral	One placebo to each supplement	Adverse events Readmissions or Emergency room visits Survival Length of Stay Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Sorensen, 2014[31] (24281905) Sorenson, 2020[32] (32391656) Europe Key Question 1 & 2 Medium	148 71 years 46% female Race NR	Gastrointestinal 10% Stage IV disease Surgery alone No NRS-2002	Single Supplement (n-3 FA-enriched ONS)) Outpatient Multiple providers Oral	Standard isocaloric and isonitrogenous ONS for 7 days before & after surgery	Adverse events Readmissions or Emergency room visits Survival Length of stay
Sultan, 2012[33] (22237467) Europe Key Question 1 & 2 Medium	195 64 years 26% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (immunoenhancing diet – Oxepa) Inpatient Provider NR Enteral	No preoperative nutritional support; enteral Osmolite for 7 days after surgery	Weight or body composition changes Adverse events Survival Length of stay
Tsuchiya, 2016[34] (27306219) Asia Key Question 1 & 2, 3 High	70 63 years 40% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Screening Tool NR	Supplements (added amino acids) Outpatient Provider NR Oral	No supplement	Adverse events Treatment tolerance
Vidal-Casariego, 2014[35] (23471208) Europe Key Question 1 & 2 Not conducted	69 67 years 35% female Race NR	Multiple cancers 7% Stage IV disease Radiation alone No Other Tool	Single Supplements (added glutamine) Outpatient Other Oral	30 mg/d oral casein (placebo) 3 days before RT until the completion of RT	Weight or body composition changes Changes in nutritional status Adverse events
Yegen, 2020[36] PMID NA Europe Key Question 1 & 2 High	78 62.9 42% female Race NR	Gastrointestinal 0% Stage IV disease Surgery No Multiple tools	Supplements (ONS with arginine, glutamine, Omega-3 fatty acid, and RNA. (3x/day) from 7 d before surgery to 30 days after (NJ tube if needed)) Inpatient Provider NR Enteral	200 ml ONS (Resource 2.0 with fiber), 3x/day from 7 d before surgery to 30 days after (NJ tube if needed	Weight or body composition changes Adverse events Survival Length of Stay

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NA = not available; WPI = whey protein isolate; ONS = oral nutritional supplement; FA = fatty acid; EPA = eicosapentaenoic acid; MST = malnutrition screening tool; TPN = total parenteral nutrition; RT = radiotherapy.

*For select studies only.

†Reports median age when mean is not available.

Route or Timing of Nutrition Interventions

Table D.2. Characteristics of included studies: route or timing of nutrition interventions delivered prior to and during cancer treatment (spans KQ 1 and 2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Braga, 2002[37] (11822956) Europe Key Question 1 & 2 Not conducted	150 65 years 44% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes Other metric	Nutrition therapy (oral diet enriched with arginine, w-3 fatty acids, and RNA) Inpatient Provider NR Other	Postoperative enteral feeding with a standard diet within 12 hours of surgery	Adverse events Length of stay
Brown, 2017[38] (28797454) Other Key Question 1 & 2 3 Not conducted	131 60 years 12% female Race NR	Head & Neck 31% Stage IV disease Multiple therapies Limited to malnourished NR Screening tool NR	Nutrition (early feeding intervention via prophylactic gastrostomy tube) Multiple settings Dietitian/nutritionist Enteral	Usual care which commenced feeding when clinically indicated	Weight or body composition changes Changes in nutritional status Readmissions or emergency room visits Length of stay Treatment tolerance Quality of life
Ding, 2015[39] (25835119) Asia Key Question 1 & 2 Not conducted	106 Age NR 34% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (preoperative EN for 1 week) Inpatient Provider NR Enteral	Early postoperative EN	Weight or body composition changes
Falewee, 2014[40] (24182765) Europe Key Question 1 & 2 Not conducted	298 59 years 16% female Race NR	Head & Neck % Stage IV disease NR Surgery alone No Multiple tools	Nutrition therapy (perioperative IMPACT) Inpatient Provider NR Other	Oral or enteral, 7 days before surgery and 7-15 days postop; Perioperative formula of IMPACT without immune nutrients = "reference diet"	Adverse events Length of stay

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Gianotti, 2002[41] (12055582) Europe Key Question 1 & 2 Not conducted	305 64 years 45% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (IV supplementation) Multiple settings Provider NR Oral	No supplementation preop, oral supplementation postop	Adverse events Length of stay
Miyata, 2012[42] (22169459) Asia Key Question 1 & 2 Not conducted	91 63 years 24% female Race NR	Gastrointestinal 38% Stage IV disease Multiple therapies No Screening tool NR	Nutrition therapy (omega 3-FAs rich nutritional supplements – enteral if unable to take orally) Setting NR Provider NR Oral	Nutrition support at 600kcal/day (parental if unable to take orally)	Weight or body composition changes Adverse events
Mudge, 2018[43] (1596002) Other Key Question 1& 2, 3 Not conducted	278 64 years 19% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Nutrition therapy (immunonutrition (pre-, peri-, and post-op)) Inpatient Physician Other	Perioperative standard nutrition	Adverse events Survival Length of stay Quality of life
Wong TX, 2022[44] (35276977) Asia Key Question 1 & 2, 3 Not conducted	91 60 years 76% female Race NR	Multiple Cancers % Stage IV disease NR Surgery Yes Screening tool NR	Group SS: ONS (milk-based formula fortified with micronutrients)for 5 to 14 days preoperatively and postoperatively until discharge Group SS-E: ONS for 5 to 14 days pre-operatively and for 90-days post-discharge Multiple settings Provider NR Oral	ONS postoperatively until discharge	Weight or body composition changes Functional status

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Wu, 2020[45] PMID NA Asia Key Question 1 & 2 Not conducted	76 60 years 32% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes Other tool	Nutrition therapy (enteral support preoperative, Nutrison Fibre postoperative) Inpatient Provider NR Enteral	Normal diet before surgery, 250-500 mL of compound amino acid injection and 400 mL of Glucose Solution, PN	Changes in nutritional status Adverse events

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NA = not available; FA = fatty acid; EN = enteral nutrition; PN = parenteral nutrition.
*For select studies only.
†Reports median age when mean is not available.

Nutrition Support Including Oral Nutrition Supplements

Table D.3. Characteristics of included studies: use of nutrition support including oral nutrition supplements prior to and during cancer treatment (spans KQ1 and 2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Bozzetti, 2000[46] (10638466) Europe Key Question 1 & 2 Medium	90 Age NR 50% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes Other metric	Nutrition therapy (special TPN) Inpatient Provider NR Parenteral	Standard central IV feeding postop	Adverse events Survival Length of stay
Chen, 2017[47] PMID NA Asia Key Question 1 & 2 Medium	120 71 years 39% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone Yes NRS-2002	Nutrition (multi-oil fat emulsion PN) Inpatient Provider NR Parenteral	No preop nutritional support	Adverse events Length of stay

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Feng, 2022[48] (34362624) Asia Key Question 1 & 2, 3 Low	126 70 years 37% female Race NR	Gastrointestinal 0% Stage IV Surgery No NR	Preoperative oral CHO 200 ml. 2-3 hr. before surgery & postoperative early oral feeding (POD1=special clear liquid but no TPN; POD2=normal diet) Hospital inpatient Provider NR Oral	Fasted pre-surgery (> 8 hrs.) + TPN x 24 hr. post-surgery; advance diet as tolerated Hospital inpatient Provider NR Oral & TPN	Adverse events Readmissions/Emergency Room Visits Symptoms
Ida, 2017[49] (28072447) Aoyama, 2019[50] (30854113) Aoyama, 2022 (35836480)[51] Asia Key Question 1 & 2 High	126 65 years 34% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening Tool NR	Supplement (Ensure like product – EPA) Setting NR Provider NR Oral	Standard diet	Weight or body composition changes Adverse events
Kong, 2018[52] (30055788) Asia Key Question 1 & 2, 3 High	144 Age NR 37% female Race NR	Gastrointestinal 7% Stage IV disease Surgery alone Yes Other tool	Nutrition (standard oral nutritional supplement (Ensure powder) for 2 weeks before gastrectomy and for 4 weeks postoperatively in malnourished patients) Multiple settings Dietitian/nutritionist Oral	Standard meals designed for post-gastrectomy patients	Weight or body composition changes Adverse events Quality of life
Lidder, 2013[53] (23406311) Europe Key Question 1 & 2 Low	120 70 years 47% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (Nutricia PreOp solution + carbohydrate supplement) Setting NR Provider NR Oral	Placebo drink given 2 hours preop equal volume of flavored water with artificial sweetener postop	Adverse events Length of Stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Moya, 2016[54] (26936601) Europe Key Question 1 & 2 Medium	128 69 years 53% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition (immune-enhancing oral supplement) Inpatient Provider NR Oral	Dietary advice	Adverse events Readmissions or emergency room visits Survival Length of stay
Poon, 2004[55] (15043519) Asia Key Question 1 & 2, 3 Not conducted	88 59 years 7% female Race NR	Other 0% Stage IV disease Chemotherapy alone No Screening tool NR	Nutrition (nutritional supplementation with BCAAs twice a day in the morning and evening in addition to the usual diet) Inpatient Provider NR Oral	Standard diet	Weight or body composition changes Adverse events Survival Functional status
Ritch, 2019[56] (30359680) North America Key Question 1 & 2 Not conducted	61 68 years 12% female Non-Hispanic White	Other % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition (Supplement – Ensure) Multiple settings Dietitian/nutritionist Oral	Twice daily servings of multivitamins for 3-4 weeks before surgery and 4 weeks after surgery	Weight or body Composition changes Adverse events Readmissions or Emergency room visits Survival Length of stay
Sanchez-Guillen, 2021[57] (34441942) Lopez-Rodriguez-Arias, 2021[58] (34579122) Europe Key Question 1 & 2 Medium	170 69.7 years 39% female Race NR	Gastrointestinal Stage IV disease NR Surgery No Other Tool (ESPEN)	Peripheral PN Peri-Olimel N4E for 4 days (1 day before surgery + 3 days after) in addition to an ERAS protocol Inpatient Provider NR Parenteral	Conventional fluid therapy 1 day before surgery; post-surgery diet per ERAS protocol	Adverse events Length of stay Survival
Sittirai, 2021[59] (34371175) Asia Key Question 1 & 2, 3 Not conducted	126 57 years 34% female Race NR	Head & Neck 87% Stage IV Surgery No Screening tool NR	ONS (Immune-enhancing diet containing arginine, glutamine, and fish oil-derived fatty acids) Inpatient Provider NR Oral	Hospital-prepared blenderized diet	Adverse events Length of stay Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Wu, 2006[60] (16688841) Asia Key Question 1 & 2 High	512 57 years 36% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes Other tool	Nutrition therapy (EN or PN preop and postop) Inpatient Provider NR Route of Administration NR	Standard oral hospital diet preop and PN in postop	Adverse events Survival Length of stay
Yan, 2021[61] (32875913) Asia Key Question 1 & 2 High	200 56 years 16% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No NRS-2002	Nutrition therapy (perioperative protein enriched EN) Inpatient Provider NR Enteral	Regular food intake (low-fat diet pre-surgery, liquid/semi-liquid diet for 7 days post-surgery)	Length of stay

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; TPN = total parenteral nutrition; NRS = nutritional risk screening; PN = parenteral nutrition; ONS = oral nutritional supplement; EN = enteral nutrition; BCAA = branched-chain amino acid.
*For select studies only.
†Reports median age when mean is not available.

Multi-Component Interventions

Table D.4. Characteristics of included studies: use of multi-component interventions prior to and during cancer treatment (spans KQ1 and 2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Baldwin, 2011[62] (21733143) Europe Key Question 1 & 2, 3 Not conducted	358 66 years 37% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone Yes Screening tool NR	Multi-modality ((1) dietary advice alone; (2) nutritional supplement alone; and (3) dietary and nutritional supplement) Outpatient Dietitian/nutritionist Oral	No intervention	Survival Quality of life

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported

Risk of Bias and Outcomes Assessment

Table D.5. Risk of bias assessment: use of dietary supplements prior to and during cancer treatment (spans KQ 1 and 2)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Haidari, 2020[24] (32219761)	8 wks	Medium	Low	High	X	X	X	High
Healy, 2017[25] (28742713)	6 months	Low	Low	High	Low	Low	High (29%)	High
Jo, 2006[27] (16927064)	Inpatient	Low	Low	High	Medium	Low	Low (0)	Medium
Oguz, 2007[28] (17573745)	Inpatient	Medium	High	High	X	X	X	High
Ryan, 2009[29] (19247018)	21 days	Low	High	X	X	X	X	High
Serrano, 2022[30] (35606184)	4 wks, 12 weeks post-surgery	Low	Low	Medium	High	Low	Low (9%)	Medium

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Sorenson 2014[31] (24281905) Sorensen 2020[32] (32391656)	30 days; 3, yr, 5 yr	Medium	Low	Low	Medium	Low	Medium 13%	Medium
Sultan 2012[33] (22237467)	Inpatient	Low	Low	Low	Low	Medium	Low (0)	Medium
Tsuchiya, 2016[34] (27306219)	28 days	Low	Medium	High	X	X	X	High
Yegen, 2020[36] PMID NA	Inpatient (post-hospital non-lab outcomes NR)	Medium	Medium	High	Medium	Low	Low (0%)	High

Note: X indicates domain not assessed due to previoiusly determined high risk of bias
Abbreviations: PMID = PubMed Identification Number; yr = year; KQ = Key Question

Table D.5.1. Outcomes assessment: use of dietary supplements prior to and during cancer treatment (low and medium ROB studies), spans KQ 1 and 2

Author, year, PMID, RoB Timing	N	Treatment	Control	Weight / Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/Emergency Room Visits	Survival	LOS	Treat. Tolerance	QOL	Symptoms	Functional Status
Jo 2006[27] (16927064) Medium Inpatient	60	Glutamine 0.2 g/kg/d in TPN postop	TPN (presumed, NR)	↑MAC ↔TSF, MAMC	NA	↔ by POD 7	NA	↔	↔	-	-	-	-
Serrano, 2022[30] 35606184 Medium 4 wks, 12 weeks post-surgery	71	Protein supplementation rich in arginine and omega-6 and carbohydrate loading	One placebo to each supplement	NA	NA	↔ Infectious complications	↔ Unplanned ER visits ↔ readmissions	↔ 90-day mortality	↔	-	-	-	-
Sorenson 2014[31] (24281905) Sorensen 2020[32] (32391656) Medium 30 days	148	Omega-3 FA enriched ONS	Standard isocaloric ONS	NA	NA	↔	Readmissions ↔	↔	↔	-	-	-	-

Author, year, PMID, RoB Timing	N	Treatment	Control	Weight / Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/Emergency Room Visits	Survival	LOS	Treat. Tolerance	QOL	Symptoms	Functional Status
Sultan 2012[33] (22237467) Medium Inpatient	195	1. IEN with omega 3 FAs 7d preop & postop 2. Standard EN for 7d preop & postop	Standard EN postop only	↔	NA	↔ count of infectious AEs ↔ % of patients. infectious AEs ↔other AEs	NA	↔	↔	-	-	-	-

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; BMI: body mass index; FFM: fat free mass; AE: adverse events; LOS: length of stay; NA=not assessed; QOL: quality of life; PRO: patient reported outcome; TPN: total parenteral nutrition; FA: fatty acid: ONS: oral nutritional supplement: EN: enteral nutrition: POD: post-operative day; IEN=immunoenteral nutrition; NR: Not reported; MAC: mid-arm circumference; TSF: triceps skin fold; MAMC: mid-arm muscle circumference; KQ = Key Question; NA=not assessed.

-: Not applicable

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer AEs, shorter LOS than comparison group)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more AEs, longer LOS)

↔: No statistically significant difference between groups

Table D.6.1. Risk of bias assessment: use of nutrition support including oral nutrition supplements prior to and during cancer treatment (spans KQ 1 and 2)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Bozzetti, 2000[46] (10638466)	10 d preop + inpatient postop	Low	Medium	Medium	Medium	Low	Low (0)	Medium
Chen, 2017[47] (616782903)	Inpatient	Low	Low	Low	Medium	Medium	Low (0)	Medium
Feng, 2022[48] (34362624)	Inpatient, 30 d	Low	Low	Medium	Medium	Low	Low (0)	Low
Ida, 2017[49] (28072447) Aoyama, 2019[50] (30854113) Aoyama, 2022[51] (35836480)	3 months	Low	Medium	High	X	X	X	High
Kong, 2018[52] (30055788)	30 days	Low	Medium	High	X	X	X	High
Lidder 2013[53] (23406311)	Inpatient, 30 days	Low	Low	Low	Medium	Low	Low (0)	Low
Moya 2016[54] (26936601)	7 d preop, inpatient, 30d	Low	Low	Medium	Medium	Low	Low 8%	Medium

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Sanchez-Guillen, 2021[57] (34441942) Lopez-Rodriguez-Arias, 2021[58] (34579122)	90 days post-surgery	Low	Medium	Medium	Medium	Low	Low (7%)	Medium
Yan, 2021[61] (32875913)	Inpatient	Medium	High	X	X	X	X	High
Wu, 2006[60] (16688841)	Inpatient	Medium	High	X	X	X	X	High

Note: X indicated domain not assessed due to previously determined high risk of bias.
Abbreviations: PMID = PubMed Identification Number; d = days; preop = preoperative; KQ = Key Question

Table D.6.2. Outcomes assessment: use of nutrition support including oral nutrition supplements prior to and during cancer treatment (low and medium ROB Studies; spans KQ 1 and 2)

Author, Year, PMID, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QOL	Symptoms	Functional Status
Bozzetti, 2000[46] (10638466) Medium Inpatient	317	Total parenteral nutrition for 10 days perioperatively and 9 days postoperatively	Standard central IV feeding postop	NA	NA	↑ complications/noninfectious complications	NA	↑	↓	-	-	-	-
Chen 2017[47] (616782903) Medium Inpatient 3d, 7d	120	1. Preop multi-oil fat emulsion PN 2. Intralipid PN	No nutritional support	NA	NA	↑ Complications	NA	NA	↔	-	-	-	-
Feng, 2022[48] (34362624) KQ 1&2, 3 Low Inpatient, 30 d	126	Preoperative oral CHO 200 ml 2-3 hr. before surgery & postoperative early oral feeding	Fasted pre-surgery (> 8 hrs.) + TPN x 24 hr. post-surgery	NA	NA	↔ complications	↑hospitalization	NA	NA	-	-	-	-

Author, Year, PMID, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QOL	Symptoms	Functional Status
Lidder, 2013[53] (23406311) Low Inpatient, 30d	120	1.Preop+postop CHO drink 2. Preop CHO drink 3. Postop CHO drink	Placebo drink preop & postop	NA	NA	↑ preop+ postop vs control in complications at 30 days	NA	NA	↔	-	-	-	-
Moya, 2016[54] (26936601) Medium Inpatient 30d	128	IEN x 7 d preop + 5 d postop	Dietary advice	NA	NA	↑ wound infection ↔ other AEs	↔	↔ (0)	↔	-	-	-	-
Sanchez-Guillen, 2021[57] (34441942) Lopez-Rodriguez-Arias, 2021[58] (34579122) Medium 90 days post-surgery	170	Peripheral parenteral nutrition 4 days (the day before the scheduled surgery and 3 days after surgery	Conventional fluid therapy	NA	NA	↔ overall AEs ↑ major AEs ↑ minor AEs ↔ SSI	NA	UTD	↔	-	-	-	-

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; BMI: body mass index; FFM: fat free mass; AE: adverse events; LOS: length of stay; QOL: quality of life; PRO: patient reported outcome; PN: parenteral nutrition; IEN=immunoenteral nutrition; UTD: unable to determine; KQ = Key Question; NA=not assessed

-: Not applicable

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer Aes, shorter LOS than comparison group)

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more Aes, longer LOS)

↔: No statistically significant difference between groups

Appendix E. Evidence Tables for Chapter 7

Nutritional Counseling

Table E.1. Characteristics of included studies: use of nutritional counseling during cancer treatment (KQ2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Bourdel-Marchasson, 2014[63] (25265392) Europe Key Question 2 Not conducted	341 78 years 49% female Race NR	Multiple cancers 7% Stage IV disease Chemotherapy alone Yes MNA-SF	Counseling only (dietary advice) Outpatient Dietitian/nutritionist Not applicable	Routine nutritional care	Weight or body composition changes Readmissions or emergency room visits Survival
Britton, 2019[64] (30296472) Other Key Question 2, 3 Not conducted	307 58 years 21% female Other	Head & Neck 65% Stage IV disease Radiation alone No Screening tool NR	Counseling only (Eating As Treatment (EAT) dietary advice) Outpatient Dietitian/nutritionist Not applicable	Treatment as usual	Weight or body composition changes Changes in nutritional status Treatment tolerance Quality of life
Forslund, 2020[65] (31758324) Europe Key Question 2, 3 Not conducted	180 67 years 0% female Race NR	Other 4% Stage IV disease Radiation alone No Screening tool NR	Counseling only (advised to increase soluble fiber and decrease lactose in diet) Outpatient Dietitian/nutritionist Not applicable	Standard care	Adverse events Quality of life
Isenring, 2004[66] (15226773) Other Key Question 2, 3 Not conducted	60 62 years 15% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies No Other tool	Counseling only (intensive nutritional counseling for up to 3 months) Outpatient Dietitian/nutritionist Not applicable	Less intensive diet education by nurses	Weight or body composition changes Changes in nutritional Status Quality of life Functional status

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Loser, 2021[67] (33766702) Europe Key Question 2 Not conducted	69 Age NR 28% female Race NR	Head & Neck 33% Stage IV disease Multiple therapies No Multiple tools	Counseling only (individualized nutritional counseling every two weeks) Outpatient Multiple providers Not applicable	Did not receive any nutritional counseling, only interim medical visits by a physician	Weight or body composition changes Changes in nutritional status Adverse events Survival
Movahed, 2020[68] PMID NA Other Key Question 2, 3 Not conducted	100 67 years 49% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Other tool	Counseling only (individualized dietary plan and nutrition education) Setting NR Other provider Not applicable	General dietary advice at the beginning of the treatment	Weight or body composition changes Changes in nutritional status Symptoms Functional status
Orell, 2019[69] (30937304) Europe Key Question 2 Not conducted	58 60 years % female NR Race NR	Head & Neck 64% Stage IV disease Multiple therapies No Other tool	Counseling only (intensive nutritional counseling) Outpatient Dietitian/nutritionist Not applicable	Baseline nutritional counseling, that included one dietetic consultation before chemoradiotherapy	Weight or body composition changes Changes in nutritional status Adverse events Survival
Pettersson, 2012[70] (22633817) Region NR Key Question 2, 3 Not conducted	130 66 years 0% female Race NR	Other % Stage IV disease NR Radiation alone No Other tool	Counseling only (advised to increase soluble fiber and decrease lactose in diet) Setting NR Dietitian/nutritionist Not applicable	Standard care (advised to continue normal diet)	Adverse events Symptoms Functional status
Qiu, 2020[71] (31526964) Asia Key Question 2, 3 Not conducted	85 67 years 36% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Multiple tools	Counseling only (whole-course nutrition management) Inpatient Multiple providers Not applicable	The control group was treated with general nutritional supplementation	Weight or body composition changes Adverse events Length of stay Quality of life Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Ravasco, 2012[72] (23134880) Europe Key Question 2, 3 Not conducted	89 64 years 46% female Race NR	Gastrointestinal % Stage IV disease NR Radiation alone No Other tool	Counseling only (individualized nutritional counseling and education about regular foods weekly for 6 weeks) Outpatient Provider NR Not applicable	Group 2: dietary supplements and consumed usual diet of regular foods Group 3: consumed usual diet of regular foods	Weight or body composition changes Changes in nutritional status Adverse events Survival Quality of life Symptoms
Regueme, 2021[73] (32435967) Europe Key Question 2, 3 Not conducted	283 77 years 50% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone Yes Other tool	Counseling only (usual care + support to increase intake) Outpatient Dietitian/nutritionist Not applicable	Usual care: received nutritional care routinely used in the cancer treatment setting	Weight or body composition changes Quality of life Symptoms Functional status
Tu, 2013[74] (23320428) Asia Key Question 2 Not conducted	537 64 years % female NR Race NR	Multiple cancers 21% Stage IV disease Cancer treatment type NR No Multiple tools	Counseling only (30 minutes of nutrition counseling and meal planning during first week post-discharge) Outpatient Dietitian/nutritionist Not applicable	No nutrition consulting or meal planning	Weight or body composition changes Changes in nutritional status
Um, 2014[75] (24906838) Asia Key Questions 2, 3 Not conducted	87 60 years 36% female Race NR	Multiple cancers % Stage IV disease NR Radiation alone Yes Other tool	Counseling only (at least 3 sessions of individualized dietary counseling concurrent with radiation) Outpatient Dietitian/nutritionist Not applicable	One routine 20-min education session by a dietitian within 4 days of starting RT	Weight or body composition changes Changes in nutritional status Survival Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
van der Werf, 2020[76] (32037284) Europe Key Questions 2, 3 Not conducted	107 65 years 37% female Race NR	Gastrointestinal 100% Stage IV disease Chemotherapy alone No Screening tool NR	Counseling only (individualized nutritional counseling) Outpatient Dietitian/nutritionist Not applicable	Usual care	Weight or body composition changes Survival Treatment tolerance Quality of life Functional status
Zhang Z, 2022[77] (34984549) Asia Key Question 2,3 Not conducted	468 60 years 42% female Race NR	Multiple Cancers 37% Stage IV disease Radiation Therapy No Multiple tools	Nutrition education (guideline-based nutrition education counseling that was tailored and dynamic) Inpatient Nurse Not applicable	No nutrition education	**Changes in nutritional status** **Treatment tolerance**

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NA = not available; MNA-SF = mini nutritional assessment – short form.
*For select studies only
†Reports median age when mean is not available

Dietary Supplements

Table E.2. Characteristics of included studies: use of dietary supplements during cancer treatment (KQ2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Cheng, 2021[78] (34395492) Asia Key Question 2 Not conducted	60 64 years 45% female Race NR	Other (Lung) 24% Stage IV disease Chemotherapy No NRS 2002	Single Supplement (Omega-3 fatty acid supplement (EPA 1.6 g/day + DHA 0.8 g/day))x 12 weeks Setting NR Provider NR Oral	Placebo gel capsule x 12 weeks	Weight or body composition changes

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Chitapanarux, 2020[79] (31146957) Asia Key Question 2 Not conducted	88 56 years 44% female Race NR	Multiple Cancers % Stage IV Disease NR Multiple therapies No Screening tool NR	Supplements (added arginine, glutamine, and fish oil supplements) Outpatient Nurse Oral	Regular diet	Readmissions or emergency room visits Survival
da Gama Torres, 2008[80] (18317456) Other Key Question 2 Not conducted	53 37 years 53% female Race NR	Other % Stage IV disease NR Multiple therapies No Screening tool NR	Single Supplements (glutamine supplemented PN) Inpatient Other Parenteral	Standard PN for 7+ days	Adverse events Survival Length of stay
de Luis, 2004[81] (15138461) Europe Key Question 2 High	90 61 years 93% female Race NR	Head & Neck 61% Stage IV disease Surgery alone No Screening tool NR	Single Supplements (enteral diet supplement with arginine and fiber) Inpatient Provider NR Enteral	Enteral diet supplement with fiber, 12 hr postop to 10+ days	Weight or body composition changes Adverse events Length of stay
de Luis, 2005[82] (15802904) Europe Key Question 2 High	73 62 years 7% female Race NR	Head & Neck 58% Stage IV disease Surgery alone No Screening tool NR	Single Supplements (2 cans/day fatty acid-enhanced oral supplement) Setting NR Provider NR Oral	2 cans/d arginine-enhanced supplement x 12 wks	Weight or body composition changes Changes in nutritional status Adverse events Survival
de Luis, 2007[83] (16929239) Europe Key Question 2 Medium	72 62 years 90% female Race NR	Head & Neck 75% Stage IV disease Surgery alone No Other metric	Single Supplements (arginine enhanced enteral supplement via NG tube) Inpatient Provider NR Enteral	Enteral/NG formula without added arginine	Weight or body composition changes Adverse events Length of stay
de Luis, 2008[84] (18700689) Europe Key Question 2 Medium	65 63 years 9% female Race NR	Head and Neck 65% Stage IV disease Surgery alone Yes Other metric	Supplements (Supplement with a high ratio of omega-3 and omega-6) Outpatient Dietitian/nutritionist Enteral	Supplement with a low ratio of omega-3 and omega-6	Weight or body composition changes Adverse events

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
de Luis, 2009[85] (31496287) Europe Key Question 2 Medium	72 62 years 20% female Race NR	Head & Neck 74% Stage IV disease Surgery alone No Screening tool NR	Supplements (enteral diet with arginine) Outpatient Provider NR Enteral	Isocaloric, isonitrogenous enteral formula	Weight or body composition changes Adverse events Length of stay
de Luis, 2010[86] (21284343) Europe Key Question 2 Medium	115 62 years 22% female Race NR	Head & Neck 71% Stage IV disease Surgery alone No Screening tool NR	Single Supplements (enteral diet with high arginine dose) Outpatient Provider NR Enteral	Enteral diet supplements with medium dose of arginine	Weight or body composition changes Adverse events Length of stay
de Luis, 2015[87] (25855918) Europe Key Question 2 High	84 62 years 25% female Race NR	Head & Neck 45% Stage IV disease Surgery alone No Screening tool NR	Supplements (One group with medium dose of arginine, another treatment group with high dose of arginine) Outpatient Provider NR Enteral	Enteral diet with a low dose of arginine (5.8 g per day)	Weight or body composition changes Adverse events Length of stay
Farreras, 2005[88] (15681102) Europe Key Question 2 Medium	66 68 years 47% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Supplements (Enteral formula with arginine, omega-3 FAS and RNA (Impact)) Inpatient Multiple providers Enteral	Control formula same timing & route (Isosource) 12 hr postop x 7 d (no other food)	Adverse events Survival Length of stay
Fietkau, 2013[89] (23765693) Europe Key Question 2, 3 Not conducted	111 56 years 16% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies No Other tool	Single Supplement (Disease-specific enteral formula (Supportan)) Outpatient Physician Enteral	500 mL of the enteral standard nutrition Fresubin energy fibre	Weight or body composition changes Changes in nutritional Status Quality of life Functional status
Golkhalkhali, 2018[90] (28857425) Asia Key Question 2, 3 Medium	140 Age NR % female NR Asian	Gastrointestinal % Stage IV disease NR Chemotherapy alone No Screening tool NR	Single Supplement (Microbial cell prep and omega-3 fatty acids) Inpatient Provider NR Oral	Placebo	Weight or body compositions changes Quality of life Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Iwase, 2016[91] (26105516) Asia Key Question 2, 3 Not conducted	59 Age NR 100% female Race NR	Other 14% Stage IV disease Chemotherapy alone No Screening tool NR	Supplements (Amino acid jelly (Inner Power) oral diet supplement) Setting NR Provider NR Oral	Regular care	Adverse events Quality of life Symptoms
Jiang, 2010[92] (20473991) Asia Key Question 2 Low	206 Age NR 35% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Single Supplements (Soybean plus fish oil emulsion) Inpatient Nurse Parenteral	Soybean oil only (PN via central catheter)	Weight or body Composition changes Adverse events Length of stay
Klek, 2005[93] (15906909) Europe Key Question 2 High	105 61 years 43% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Other metric	Supplements (One group PN and glutamine, another treatment group PN and Omega 3-FA (Omegaven)) Setting NR Provider NR Enteral	Standard PN	Weight or body composition changes Changes in nutritional Status Length of stay
Lobo, 2006[94] (16777271) Adiamah, 2021[95] (34656029) Europe Key Question 2 Low	120 66 years 23% female Race NR	Gastrointestinal 0% Stage IV Disease Surgery alone No Screening tool NR	Supplements (Higher arginine, glutamine, cysteine and Omega-3-FAs (Stresson)) Inpatient Provider NR Enteral	Standard isocaloric, isonitrogenous diet	Adverse events Survival Length of stay
Lu, 2011[96] (21396307) Asia Key Question 2 Medium	50 67 years 32% female Race NR	Gastrointestinal 16% stage IV disease Surgery alone No Screening tool NR	Single Supplements (Glutamine enriched TPN) Inpatient Physician Parenteral	Standard TPN with 1.5 gm/kg/day of amino acids solution	Adverse events
Matsuda, 2017[97] (28138734) Asia Key Question 2 High	87 64 years 25% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Screening tool NR	Single Supplements (Diet enriched with EPA, GLA and antioxidants) Inpatient Provider NR Enteral	Standard isocaloric, isonitrogenous diet	Weight or body composition changes Adverse events Survival Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Miyata, 2017[98] (27644137) Asia Key Question 2 Medium	61 65 years 15% female Race NR	Gastrointestinal 23% Stage IV disease Chemotherapy alone No Screening tool NR	Single Supplements (Omega-3 rich EN support) Setting NR Physician Enteral	Omega-3 poor EN support	Weight or body composition changes Adverse events
Pathak, 2019[99] (31410338) Asia Key Question 2 Medium	60 Age NR 10% female Race NR	Head & Neck % Stage IV disease NR Multiple therapies No Screening tool NR	Single Supplements (glutamine supplementation) Setting NR Provider NR Oral	No glutamine	Weight or body composition changes Adverse events Readmissions or emergency room visits
Pottel, 2014[100] (25293388) Europe Key Question 2 Medium	85 61 years 16% female Race NR	Head & Neck % Stage IV Disease NR Multiple therapies No Other tool	Supplements (echium oil supplementation twice daily for 7 weeks) Setting NR Multiple providers Oral	Received a placebo, containing the same volume of n-3 PUFA deficient sunflower oil (Sunflower Oil High Oleic)	Weight or body composition changes Changes in nutritional Status Adverse events
Sun, 2008[101] (18376691) Asia Key Question 2 Medium	64 65 years 31% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone Yes Other tool	Single Supplement (BCAA enriched TPN) Inpatient Provider NR Parenteral	Standard TPN from POD 1-6	Weight or body composition changes Adverse events Survival
Takeshita, 2009[102] (19285598) Asia Key Question 2 Medium	58 70 years 29% female Race NR	Gastrointestinal % Stage IV disease NR Chemotherapy alone No Screening tool NR	Single Supplements (snack with 50 g of BCAA for 14 days) Outpatient Provider NR Oral	No BCAA snack	Weight or body composition changes Survival Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Tanca, 2009[103] PMID NA Europe Key Question 2, 3 Not conducted	475 62 years 40% female Race NR	Multiple cancers 95% Stage IV disease Cancer treatment type NR Yes Multiple tools	Supplements (5 treatment groups: 1) Progestational agent, 2) EPA, 3) L-carnitine, 4) Thalidomide, 5) Progestational agent plus pharmacologic nutritional support and L-carnitine and thalidomide) Other Provider NR Oral	No placebo or control	Weight or body composition changes Quality of life Symptoms Functional status
Tumas, 2020[104] (32184025) Europe Key Question 2 Not conducted	70 63 years 47% female Race NR	Other 0% Stage IV disease Surgery alone No NRS-2002	Supplements (Supplemented with arginine (Cubitan Nutricia) for 5 days) Outpatient Provider NR Oral	Unclear	Changes in nutritional Status Adverse events
Wang, 2017[105] (28927119) Asia Key Question 2, 3 High	94 59 years 37% female Race NR	Gastrointestinal 100% Stage IV disease Multiple therapies No Screening tool NR	Single Supplements (glutamine enriched nutritional support) Inpatient Provider NR Parenteral	Basic nutritional support	Adverse events Quality of life
Wang, 2013[106] (24379010) Asia Key Question 2 Low	94 58 years 24% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No NRS-2002	Single Supplements (EN with PN containing olive-oil based lipid emulsion) Inpatient Provider NR Parenteral	EN with medium/long chain triglyceride emulsion based PN after tumor resection for ≥7 days	Adverse events Survival Length of stay
Wang, 2010[107] (21208095) Asia Key Question 2, 3 Medium	229 56 years 36% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Supplements (EN enriched with medium-chain triglycerides and protein) Inpatient Multiple providers Enteral	Isocaloric EN for ≥5 days started within 48-72 h post-surgery	Adverse events Length of stay Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Wu, 2012[108] (23554777) Asia Key Question 2 High	63 52 years 21% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Single Supplements (TPN with omega-3 supplement) Inpatient Provider NR Parenteral	TPN with soybean oil (not omega 3) for >5 days	Adverse events Survival Length of stay
Yang, 2022[109] (35500316) Asia Key Question 2 Medium	120 59 years 32% female Race/Ethnicity NR	Gastrointestinal 0% Stage IV disease Surgery No Screening tool NR	Nutrition support: EN (NJ tube started POD 2) & (PN with n-3 fatty acids POD 1-5) Inpatient Provider NR EN + PN	Nutrition support: EN (NJ tube started POD 2) & PN	Adverse events Readmissions/Emergency room visits Length of stay Survival
Yeh, 2013[110] (23562359) Asia Key Question 2 High	68 54 years 1% female Race NR	Head & Neck 79% Stage IV diseaseRadiation alone Yes Screening tool NR	Single Supplements (Nutritional supplement including omega-3 fatty acids, glutamine, selenium for 3 months) Outpatient Multiple providers Oral	Isocaloric supplementation for 3 mo. (2 mo. during treatment, 1 mo. After)	Weight or body composition changes
Zhang, 2017[111] (27614675) Asia Key Question 2 Not conducted	320 49 years 27% female Race NR	Other 11% Stage IV Disease Surgery alone Yes NRS-2002	Single Supplements (PN supplemented with omega-3 fatty acids) Inpatient Provider NR Parenteral	Standard TPN starting on POD 1 for 5 consecutive days	Adverse events Survival Length of stay
Zhu, 2012[112] (22340541) Asia Key Question 2 Low	57 70 years 42% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Single Supplements (PN with fish oil and soybean oil) Inpatient Provider NR Parenteral	PN POD 1-8 (1.2 g/kg soybean oil)	Adverse events Length of stay

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; FA = fatty acid; PN = parenteral nutrition; EN = enteral nutrition; TPN = total parenteral nutrition; POD = post-operative day; EPA = eicosapentaenoic acid; NRS = nutritional risk screening; BCAA = branched-chain amino acid; PUFA = polyunsaturated fat; GLA = c-linolenic acid; MNA-SF = Mini Nutritional Assessment – Short Form; NG = nasogastric.

*****For select studies only.

†Reports median age when mean is not available.

Special Diets

Table E.3. Characteristics of included studies: use of special diets during cancer treatment (KQ2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Gardner, 2008[113] (18955453) North America Key Question 2, 3 Not conducted	153 64 years % female NR Race NR	Other % Stage IV disease NR Chemotherapy alone No Screening tool NR	Special Diets (diet with raw fruits and vegetables) Inpatient Provider NR Oral	Diet without raw fruits & vegetables	Weight or body composition changes Adverse events Survival Symptoms
Ingersoll, 2010[114] (20189927) North America Key Question 2, 3 Not conducted	77 54 years 81% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone No Screening tool NR	Special Diets (standard medical CINV management + grape juice) Outpatient Provider NR Oral	Standard medical CINV management	Adverse events Quality of life Symptoms
Jatoi, 2016[115] (27039205) North America Key Question 2, 3 Not conducted	118 Age NR 52% female Race NR	Other 100% Stage IV disease Multiple therapies No Screening tool NR	Special Diets (white wine twice daily) Outpatient Provider NR Oral	Nutritional supplement like boost or ensure	Adverse events Quality of life Functional status
Khodabakhshi, 2020[116] (314996287) Khodabakhshi, 2020[117] (32828130) Other Key Question 2, 3 Not conducted	80 Age NR 100% female Race NR	Other 26% Stage IV disease Chemotherapy alone No Screening tool NR	Special Diets (ketogenic) Outpatient Dietitian/nutritionist Oral	Standard diet	Weight or body composition changes Quality of life
Lugtenberg, 2021[118] (33179154) Europe Key Question 2, 3 Not conducted	129 50 years 100% female Race NR	Other % Stage IV disease NR Chemotherapy alone No Screening tool NR	Special Diets (calorie content declined for 3 days before and the day of treatment) Setting NR Physician Other	Regular diet	Weight or body composition changes Quality of life Symptoms Functional status

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Miyakawa, 2019[119] (30554216) Asia Key Question 2, 3 Not conducted	100 71 years 66% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Special Diets (rice porridge) Inpatient Provider NR Oral	Liquid diet with gradual transition to solid food	Length of stay Quality of life Symptoms
Voss, 2020[120] (32619561) Europe Key Question 2, 3 Not conducted	50 57 years % female NR Race NR	Other % Stage IV disease NR Radiation alone No Screening tool NR	Special Diets (3 days of ketogenic diet, 3 days of intermittent fasting, then 3 days of ketogenic diet) Outpatient Dietitian/nutritionist Oral	Calorically unrestricted diet	Survival Symptoms
Wedlake, 2012[121] (1605807) Europe Key Question 2, 3 Not conducted	117 65 years 32% female Race NR	Multiple cancers % Stage IV disease NR Radiation alone No Screening tool NR	Special Diets (Low fat and moderate fat intake) Outpatient Provider NR Oral	Normal fat (LCT – 40% of total energy)	Weight or body composition changes Quality of life Symptoms Functional status

Abbreviations: KQ = key question; PMID = PubMed Identification Number; NR = not reported; CINV = hemotherapy-indKKuced nausea and vomiting; LCT = long chain triglycerides.

*For select studies only.

†Reports median age when mean is not available.

Route or Timing of Nutritional Interventions

Table E.4. Characteristics of included studies: route or timing of nutritional interventions during cancer treatment (KQ2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Berkelmans, 2020[122] (31090563) Europe Key Question 2 Medium	148 65 years 14% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (started directly with a liquid oral diet starting on the day of surgery) Inpatient Physician Oral	Delay in start of oral intake; only allowed to drink clear liquids; received tube feeding	Weight or body composition changes Changes in nutritional status Adverse events Readmissions or emergency room visits Survival Length of Stay
Boelens, 2014[123] (24169163) Europe Key Question 2 High	123 65 years 32% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Screening tool NR	Nutrition therapy (EEN) Inpatient Physician Other	EPN	Adverse events Length of stay
Bozzetti, 2001[124] (11705560) Europe Key Question 2 Low	317 65 years 42% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes Other metric	Nutrition therapy (enteral nutrition postop) Inpatient Provider NR Enteral	Parenteral nutrition postop	Adverse events Survival Length of stay
Braga, 2001[125] (11246300) Europe Key Question 2 Medium	257 64 years 46% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Nutrition therapy (EEN postop until oral intake was GE 800 kcal/day) Inpatient Provider NR Enteral	TPN postop until oral intake was GE 800 kcal/cay	Adverse events Survival Length of stay
Dag, 2011[126] (22189721) Asia Key Question 2 High	199 62 years 43% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (early oral feeding) Inpatient Provider NR Oral	Fasted until first flatus or stools	Adverse events Length of stay

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Feo, 2004[127] (15144242) Europe Key Question 2, 3 Medium	100 68 years % female NR Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (clear oral liquids) Inpatient Provider NR Oral	Fasting until passage of flatus then NG diet	Adverse events Survival Length of stay Symptoms
Gao, 2019[128] (30941970) Asia Key Question 2 High	198 55 years 38% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (oral fluid diet started on the POD 2) Inpatient Provider NR Oral	Nasogastric tube 30 min before surgery until the recovery of gastrointestinal function	Adverse events
Huang, 2015[129] (1594390) Asia Key Question 2 High	105 Age NR 35% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No MNA	Nutrition therapy (EEN) Setting NR Provider NR Other	TPN and EN + PN	Changes in nutritional status Adverse events Length of stay
Hyltander, 2005[130] (15880316) Europe Key Question 2 High	126 62 years 34% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	(PN and EN) Multiple settings Multiple providers Other	Standard oral solution	Weight or body composition changes Changes in nutritional status Adverse events Survival
Kita, 2021[131] (33526287) Asia Key Question 2 High	91 Age NR 22% female Race NR	Gastrointestinal 35% Stage IV disease Chemotherapy alone No Screening tool NR	Nutrition therapy (EN) (added triglycerides/fatty acids) Setting NR Provider NR Oral	Parenteral nutrition	Weight or body composition changes Adverse events

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Kurbanalievich, 2020[132] PMID NA Asia Key Question 2 Medium	80 Age NR 45% female Race NR	Gastrointestinal % Stage IV disease NR Cancer treatment type NR Limited to malnourished NR Multiple tools	Nutrition therapy (EN from POD 2) Inpatient Provider NR Enteral	Isolated parenteral nutrition from POD 1	Weight or body composition changes
Li, 2015[133] (26011337) Asia Key Question 2 High	400 Age NR 46% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (EEN for 7 days) Inpatient Provider NR Enteral	Postoperative parenteral nutrition for 7 days	Changes in nutritional status Length of stay
Liu, 2011[134] (21669582) Asia Key Question 2 Not conducted	58 Age NR 43% female Race NR	Other % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (EN at least 6 days postop) Inpatient Provider NR Enteral	TPN formulas for 7 days postop, until the TPN was completely replaced by oral intake	Changes in nutritional status Adverse events Length of stay
Luo, 2018[135] (28666095) Asia Key Question 2 High	78 62 years 21% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (EEIN) Inpatient Provider NR Other	Parenteral nutrition	Weight or body composition changes Adverse events Survival Length of stay
Ma, 2020[136] (33362392) Asia Key Question 2 Medium	60 59 years 41% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes NRS-2002	Nutrition therapy (EEN) Inpatient Physician Enteral	Postoperative total parenteral nutrition	Adverse events Length of stay
Mahmoodzadeh, 2015[137] (24875466) Asia Key Question 2 High	109 65 years 47% female Race NR	Gastrointestinal 4% Stage IV disease Multiple therapies No Screening tool NR	Nutrition therapy (early oral feeding) Inpatient Physician Oral	Late oral feeding (kept nil per os)	Adverse events Readmissions or emergency room visits Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Minig, 2009[138] (19760046) Europe Key Question 2 Not conducted	143 56 years 100% female Race NR	Multiple cancers % Stage IV disease NR Surgery alone No Other tool	Nutrition therapy (early oral feeding) Inpatient Physician Oral	Traditional oral feeding	Adverse events Length of stay
Perinel, 2016[139] (27429039) Europe Key Question 2 High	204 65 years 39% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Nutrition therapy (EEN POD 1) Inpatient Provider NR Enteral	TPN starting on POD 1 and continued until oral intake reached 60% of nutritional requirements	Adverse events Survival Length of stay
Roberts, 2003[140] (13130320) North America Key Question 2, 3 Not conducted	55 44 years 100% female Race NR	Other 58% Stage IV disease Multiple therapies No Multiple tools	Nutrition therapy (TPN) Inpatient Provider NR Parenteral	Oral diet post-surgery with IV fluids	Weight or body composition changes Adverse events Length of stay Quality of life
Ryu, 2009[141] (19255706) Asia Key Question 2 Not conducted	81 64 years 11% female Race NR	Head & Neck 31% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (nasogastric tube nutrition) Inpatient Dietitian/nutritionist Enteral	Total parenteral nutrition commenced 24h after surgery	Weight or body composition changes Adverse events Length of stay
Sadasivan, 2012[142] (22973911) Asia Key Question 2, 3 Not conducted	100 Age NR % female NR Race NR	Head & Neck 50% Stage IV Disease Multiple therapies No Screening tool NR	Nutrition therapy (percutaneous endoscopic gastrostomy) Setting NR Multiple providers Enteral	Nasogastric tube administration	Weight or body composition changes Adverse events Treatment tolerance
Seven, 2003[143] (12782826) Asia Key Question 2 Not conducted	67 56 years 8% female Race NR	Head & Neck % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition therapy (clear liquid diet began POD 1) Inpatient Provider NR Oral	Tracheoesophageal puncture feeding, oral began POD 7	Adverse events Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Sousa, 2014[144] (24736040) Other Key Question 2 Not conducted	89 63 years 8% female Race NR	Head & Neck 97% Stage IV diseaseSurgery alone No Other tool	Nutrition therapy (early oral feeding beginning 24 hr after postop) Inpatient Provider NR Oral	Late oral feeding (began postop day 7)	Adverse events
Sun, 2018[145] (28549015) Asia Key Question 2, 3 Medium	280 63 years 30% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No NRS-2002	Nutrition therapy (early oral feeding starting on POD 1) Inpatient Multiple providers Oral	Late oral feeding starting on POD 7	Weight or body composition changes Adverse events Survival Length of stay Quality of life Symptoms
Tao, 2020[146] (31512101) Asia Key Question 2, 3 Medium	120 64 years 52% female Race NR	Gastrointestinal 11% Stage IV diseaseSurgery alone No Screening tool NR	Nutrition therapy (jejunostomy feeding starting on POD 1 until 3 wks past discharge) Inpatient Provider NR Enteral	Nasogastric feeding starting on POD 1 until discharge	Weight or body composition changes Adverse events Survival Quality of life
van Barneveld, 2016[147] (26937858) Europe Key Question 2 High	123 64 years 32% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No MUST	Nutrition therapy (EEN) Inpatient Physician Enteral	EPN (jugular vein catheter) followed by parenteral nutrition	Adverse events Length of stay
Wang, 2019[148] (31239762) Asia Key Question 2 Medium	100 54 years 29% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No NRS-2002	Nutrition therapy (early oral feeding POD1) Inpatient Physician Oral	Delayed oral feeding starting on POD 4	Adverse events Survivall
Wang, 2018[149] (29896256) Asia Key Question 2 Medium	129 48 years 49% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (EEN within 24 h after operation) Inpatient Provider NR Other	Total parenteral nutrition	Weight or body compostion changes Adverse events Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Xiao-Bo, 2014[150] (24504222) Asia Key Question 2 Medium	120 64 years 30% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes Other tool	Nutrition therapy (EN for 7 days starting on POD 1) Inpatient Provider NR Enteral	PN for 7 days postoperatively	Adverse events Length of stay
Xu, 2020[151] PMID NA Asia Key Question 2 High	108 53 years 44% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (EN 2 days post op) Inpatient Provider NR Enteral	PN postop, half total amount on the first day and full amount on the next day	Changes in nutritional status
Zhang, 2019[152] (31551229) Asia Key Question 2 High	140 67 years 36% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (PN for 7 days) Inpatient Provider NR Parenteral	Central venous catheter support for 7 days	Weight or body composition changes Adverse events Length of stay

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NA = not available; NRS = nutrition risk screening; MUST = malnutrition universal screening tool; EEN = early enteral nutrition; EPN = early parenteral nutrition; TPN = total parenteral nutrition; EN = enteral nutrition; PN = parenteral nutrition; EEIN = early enteral immunonutrition; POD = post operative day.

*For select studies only.

†Reports median age when mean is not available.

Nutrition Support Including Oral Nutrition Supplements

Table E.5. Characteristics of included studies: use of nutrition support including oral nutrition supplements during cancer treatment (KQ2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Akita, 2019[153] (314451252) Asia Key Question 2 Not conducted	62 67 years 56% female Race NR	Other % Stage IV disease NR Multiple therapies Yes Screening tool NR	Nutrition (2 bottles (440ml) per day (560 kcal/day) of EPA-enriched nutritional supplement) Outpatient Provider NR Oral	Received nutritional guidance three times - immediately before, at 3 weeks and immediately after radiotherapy	Weight or body composition changes Adverse events
Baker, 2015[154] (25827292) Other Key Question 2, 3 Not conducted	109 63 years 100% female Race NR	Other 10% Stage IV disease Multiple therapies Yes Other tool	Nutrition (intraoperative nasojejunal tube placement and enteral feeding until adequate oral intake could be maintained) Inpatient Multiple providers Enteral	Postoperative diet as tolerated	Adverse events Length of stay Quality of life
Barlow, 2011[155] (21601319) Europe Key Question 2 Medium	121 64 years 32% female Race NR	Gastrointestinal 3% Stage IV disease Multiple therapies No Screening tool NR	Nutrition (early enteral nutrition was delivered via a needle catheter jejunostomy) Inpatient Physician Oral	Kept nil by mouth	Adverse events Readmissions or Emergency room visits Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Bouleuc, 2020[156] (32212354) Europe Key Question 2, 3 Not conducted	148 66 years 55% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies Yes Screening tool NR	Nutrition (parenteral nutrition was administered by central venous route using industrial ternary preparations and systematic daily addition of polyvitamins, trace elements, and electrolytes (sodium, potassium, vitamin K, magnesium, phosphorus), adapted as required) Inpatient Dietitian/nutritionist Parenteral	Oral feeding	Weight or body composition changes Adverse events Survival Quality of life
Cereda, 2018[157] (29111172) Europe Key Question 2, 3 Not conducted	159 65 years 28% female Race NR	Head & Neck 29% Stage IV disease Multiple therapies No Screening tool NR	Nutrition (2 bottles/day 250 mL of a ready-to-use energy-dense, high-protein, omega-3 enriched oral formula plus counseling) Outpatient Dietitian/nutritionist Oral	Counseling only	Weight or body composition changes Treatment tolerance Quality of life
Chen, 2021[158] (33545764) Asia Key Question 2 Not conducted	60 70 years 13% female Race NR	Other Stage IV disease NR Multiple therapies No Other tool	Nutrition (orally administered enteral nutrition (Ensure) with regular diet Outpatient Provider NR Oral	Regular diet only	Changes in nutritional status
Chen T, 2021[159] (34237976) Asia Key Question 2, 3 High	106 68 years 21% female Race/ethnicity NR	Gastrointestinal 0% Stage IV disease Surgery No NRS 2002	Post-hospital enteral nutritional emulsion via J-tube: 200-500 ml x 3-6x/day Outpatient (Home) Patient-delivered but directed by doctor, nurse & nutritionist J-tube x 1 month Enteral	Post-hospital gradual transition to soft to regular diet after 1 month (J tube in place x 1 mo, not used at home)	Weight or body composition changes Changes in nutritional status Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Chu, 2018[160] (622367981) Asia Key Question 2 Medium	98 63 years 43% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No NRS-2002	Nutrition (enteral and parenteral nutritional interventions) Inpatient Provider NR Other	Only received routine parenteral nutritional intervention	Changes in nutritional status Adverse events Length of stay
Deibert, 2016[161] (27402372) North America Key Question 2 Not conducted	102 Age NR 18% female Other	Other 1% Stage IV Disease Surgery alone No Screening tool NR	Nutrition (clear liquid diet POD 1, access to regular diet POD 2 & beyond) Inpatient Provider NR Oral	Standard postoperative care not part of a specific fast-track pathway, including nothing by mouth status until either flatus or a bowel movement, whichever occurred first	Adverse events Readmissions or emergency room visits Survival Length of stay
Faccio, 2021[162] (32363940) Other Key Question 2, 3 Not conducted	85 59 years 60% female Race NR	Multiple Cancers % Stage IV disease NR Chemotherapy alone No Screening tool NR	Nutrition (nutritional supplement with counseling) Outpatient Dietitian/nutritionist Oral	Nutritional counseling alone	Weight or body composition changes Adverse events Quality of life
Gavazzi, 2016[163] (27391922) Europe Key Question 2, 3 High	79 Age NR 38% female Race NR	Gastrointestinal 0% Stage IV disease Multiple therapies Yes NRS-2002	Nutrition (home enteral nutrition) Inpatient Multiple providers Enteral	Specific nutritional indications including total energy and protein requirements were provided	Weight or body composition changes Treatment tolerance Quality of life
Huang, 2020[164] (33032180) Asia Key Question 2, 3 Not conducted	114 50 years 27% female Asian	Head & Neck 0% Stage IV disease Multiple therapies No NRS-2002	Nutrition (prophylactic oral nutritional supplements) Other Dietitian/nutritionist Oral	Regular diet	Weight or body composition changes Changes in nutritional status Adverse events Survival Treatment tolerance Quality of life Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Imamura, 2016[165] (27084538) Kimura, 2019[166] (31788653) Asia Key Question 2 High	112 Age NR 29% female Race NR	Gastrointestinal 1% Stage IV disease Surgery alone No Screening tool NR	Nutrition (oral elemental diet post-surgery 6-8 weeks) Outpatient Provider NR Oral	Regular diet	Weight or body composition changes Adverse events
Jiang, 2018[167] (30633580) Asia Key Question 2, 3 Not conducted	100 Age NR 31% female Race NR	Head & Neck 57% Stage IV disease Multiple therapies No Other tool	Nutrition (oral nutritional supplement) Outpatient Multiple providers Oral	No oral nutritional supplement	Weight or body Composition changes Changes in nutritional Status Adverse events Quality of life
Jin, 2018[168] (30205371) Asia Key Question 2, 3 High	80 Age NR 26% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other metric	Nutrition (PN day 1 POD to 4-8 POD) Inpatient Provider NR Parenteral	Isotonic electrolyte solution	Changes in nutritional Status Quality of life
Kanat, 2013[169] (23748819) Europe Key Question 2, 3 Not conducted	69 60 years 14% female Race NR	Multiple Cancers 70% Stage IV disease Multiple therapies No Screening tool NR	Nutrition ((1) megesterol acetate (MA) plus meloxicam; (2) MA plus meloxicam plus oral eicosapentaenoic acid (EPA)-enriched nutritional supplement or (3) meloxicam plus oral EPA-enriched nutritional supplement Outpatient Provider NR Oral	*No control (three treatment groups)	Weight or body composition changes Adverse events Quality of life
Katada, 2021[170] (33009977) Asia Key Question 2 High	80 Age NR 15% female Race NR	Gastrointestinal % Stage IV Disease NR Multiple therapies No Screening tool NR	Nutrition (elemental supplementary group received ELENTAL® (160 g/day) orally 9 weeks after the start of chemotherapy Setting NR Multiple providers Oral	Non-supplemental group	Changes in nutritional status Adverse events

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Klek, 2008[171] (18571296) Klek, 2011[172] (21074910) Klek, 2017[173] (28336107) Europe Key Question 2 Low	196 61 years 37% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition (Enteral feeding was commenced 6 h after operation or the first 12 h, followed by infusion of Peptisorb or Reconvan until 7th day) Setting NR Provider NR Enteral	Oligopeptic, isocaloric diet	Adverse events Survival
Klek, 2011[174] (21820770) Klek, 2014[175] (24178182) Europe Key Question 2 Medium	167 61 years 45% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone Yes Other metric	Nutrition (immunomodulating enteral group received Stresson; immunomodulating parenteral group received Omegaven) Inpatient Provider NR Oral	Standard enteral group oligopeptic diet Peptisorb; standard parenteral group	Adverse events Survival Length of stay
Li, 2015[176] (26125924) Asia Key Question 2 High	300 Age NR 50% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition (500 mL of fractionated oral enteral nutrition) Inpatient Provider NR Oral	Traditional perioperative treatment nasoenteral feeding tube and postoperative IV)	Changes in nutritional status Adverse events Length of stay
Li C, 2020[177] PMID NA Asia Key Question 2 Medium	78 62 years 45% female Race NR	Gastrointestinal 9% Stage IV disease Chemotherapy alone No Screening tool NR	Nutrition (enteral nutrition beginning on first day of treatment for 1 course of chemo) Inpatient Provider NR Enteral	Conventional nutrition support	Adverse events Survival
Lyu, 2022[178] (35280748) Asia Key Question 2, 3 High	222 Age NR 21% female Race NR	Gastrointestinal 0% Stage IV disease Multiple therapies No Multiple tools	Nutrition (enteral nutrition with ONS (Nutrison (Nutricia)) Outpatient Nutrition support team (clinicians, nutritionists, pharmacologists and nutrition nurses) Oral	Unsystematic nutrition based on general eating conditions, blood tests & treatment toxicities	Weight or body composition changes Adverse events Survival Treatment Tolerance

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
McGough, 2008[179] (18315590) Europe Key Question 2 Not conducted	50 60 years 58% female Race NR	Multiple cancers % Stage IV disease NR Radiation alone No Screening tool NR	Nutrition (patients in the intervention group were asked to replace one meal per day, equivalent to 33% of total caloric requirements, with elemental diet. A selection of E028 Extra ready to drink 250 mL cartons and E028 Extra flavoured powder sachets were provided) Setting NR Provider NR Oral	No intervention (ie, habitual diet during radiotherapy treatment)	Adverse events
Meng, 2021[180] (32563598) Tan, 2021[181] (32563599) Asia Key Question 2, 3 Low	353 60 years 32% female Race NR	Gastrointestinal 7% Stage IV disease Surgery alone Yes NRS-2002	Nutrition (Oral nutritional supplements with dietary advice) Other Provider NR Oral	Dietary advice alone	Weight or body composition change Treatment tolerance Symptoms
Miyazaki, 2021[182] (33835329) Asia Key Question 2 Medium	1003 67 years 35% female Race NR	Gastrointestinal 3% Stage IV disease Surgery alone No Screening tool NR	Nutrition (oral nutritional supplement) Inpatient Physician Oral	Regular diet without oral nutritional supplement	Weight or body composition changes Adverse events
Nie, 2021[183] (35035754) Asia Key Question 2 High	97 59 years 42% female Race/ethnicity NR	Gastrointestinal 0% Stage IV disease Surgery No Screening tool NR	Oral enteral nutrition started 6-24 hour after surgery: 250 mL 5% glucose saline orally; EN POD 1 to 30 mL/kg/d Inpatient Provider NR Enteral	Parenteral nutrition (same calorie totals as Intervention group) Timing NR	Weight or body composition changes Adverse events Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Ohkura, 2019[184] (30169605) Asia Key Question 2 High	67 Age NR 15% female Race NR	Gastrointestinal 15% Stage IV disease Surgery alone No Multiple tools	Nutrition (6 days of postoperative supplementation of the oligomeric formula) Inpatient Physician Enteral	6 days of postoperative supplementation of the polymeric formula	Weight or body composition changes Changes in nutritional status Adverse events Length of stay
Okabayashi, 2011[185] (20852905) Asia Key Question 2, 3 High	96 67 years 70% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition (carbohydrate- and BCAA-enriched softpowder nutrient mixture) Inpatient Multiple providers Oral	Conventional diet with no supplementation	Weight or body composition changes Quality of life
Ravasco, 2005[186] (15920748) Ravasco, 2005[187] (15684319) Europe Key Question 2, 3 Not conducted	75 Age NR % female NR Race NR	Head & Neck % Stage IV disease NR Radiation alone No Other tool	Nutrition ((1) diet plus regular food; (2) regular diet plus oral nutritional supplement) Outpatient Dietitian/nutritionist Oral	Regular food	Weight or body composition changes Changes in nutritional status Treatment tolerance Quality of life Symptoms
Sanchez-Lara, 2014[188] (24746976) Other Key Question 2, 3 Not conducted	92 60 years 53% female Race NR	Other 62% Stage IV disease Chemotherapy alone No Other tool	Nutrition (oral nutritional supplement EPA) Setting NR Provider NR Oral	Standardized diets of 1400, 1600, 1800, 2000, or 2200kcal.	Weight or body composition changes Adverse events Survival Quality of life Symptoms Functional status
Scislo, 2018[189] (29533110) Europe Key Question 2 High	98 63 years 28% female Race NR	Gastrointestinal 23% Stage IV disease Surgery alone No Other metric	Nutrition (postoperative immunomodulating enteral nutrition) Inpatient Provider NR Enteral	Standard enteral nutrition	Adverse events Survival
Shimizu, 2018[190] (29721714) Asia Key Question 2 High	187 66 years 37% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition (early oral feeding with iEAT (POD 1-3)) Inpatient Provider NR Oral	Conventional nutritional management	Adverse events Readmissions or emergency room visits Length of stay

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Sim, 2022[191] (35225460) Asia Key Question 2,3 High	58 64 years 20% female Race NR	Gastrointestinal 63% Stage IV disease Chemotherapy No Other tool	ONS twice a day (400ml, 400kcal) along with nutrition counseling and education Outpatient Multiple providers Oral	Nutrition counseling and education along with a weekly call from a trained dietitian	Changes in nutritional status Quality of Life Symptoms
Vidal, 2016[192] (27770454) Europe Key Question 2, 3 Not conducted	157 66 years 34% female Race NR	Other 8% Stage IV disease Surgery alone No Screening tool NR	Nutrition (TPN (Nutriflex special 70/240) for 5 days starting within 24 h after surgery) Outpatient Provider NR Parenteral	Oral nutrition alone started on day of surgery	Weight or body composition changes Survival Quality of life Functional status
Wang J, 2022 (35126900)[193] Asia Key Question 2, 3 High	80 43 years 43% female Race NR	Gastrointestinal 0% Stage IV disease Multiple therapies No Screening Tool NR	Enteral nutrition (Early enteral nutrition via nasointestinal tube 12-24 hours after surgery continuously for 7 days post surgery) Inpatient Provider NR Enteral	No enteral nutrition	Adverse events Length of stay Functional status
Wu, 2017[194] (27208039) Asia Key Question 2, 3 Medium	73 56 years 32% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition (EN + PN for ≥7 days; EN started within 24 hr postsurgery) Inpatient Provider NR Parenteral	EN alone for ≥7 days started within 24 hr postsurgery	Weight or body composition changes Adverse events Length of stay Quality of life
Xie, 2021[195] (34988183) Asia Key Question 2, 3 Medium	77 62 years 19% female Race NR	Gastrointestinal 0% Stage IV disease Surgery No Screening tool NR	Intervention type (300 mL oral nutritional supplement in addition to standard diet) Other Provider NR Oral	Regular diet alone	Weight or body composition changes Adverse events Readmissions/emergency room visits Survival Length of Stay Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Yang, 2020[196] (32833549) Asia Key Question 2, 3 High	120 64 years 23% female Race NR	Gastrointestinal 61% Stage IV disease Radiation alone No NRS-2002	Nutrition (nutritional counseling and dietary advice + oral nutritional supplement) Outpatient Multiple providers Oral	Nutritional counseling and dietary advice	Weight or body composition changes Changes in nutritional status Adverse events Symptoms
Yao, 2019[197] (31646824) Asia Key Question 2 Medium	114 65 years 40% female Race NR	Gastrointestinal 0% Stage IV disease Multiple therapies No Screening tool NR	Nutrition (early enteral nutrition support) Inpatient Multiple providers Enteral	Routine nutritional support	Adverse events Length of stay
Zhang Y, 2022[198] (35811605) Asia Key Question 2 Not conducted	82 69 years 37% female Race NR	Other (Lung) % Stage IV disease NR Surgery No MNA	Nutrition (Enteral nutrition support: a nasogastric tube was placed and whole protein enteral nutrition was infused with an initial amount of 750 kcal/d at 38˚C via a nutrition pump at a controlled rate of 70–150ml/h.) Inpatient Provider NR Enteral	Parenteral nutrition	Weight or body composition changes Changes in nutritional status Adverse Events Survival
Zhao, 2014[199] PMID NA Asia Key Question 2 Not conducted	64 33 years 22% female Race NR	Other % Stage IV Disease NR Chemotherapy alone No NRS-2002	Nutrition (enteral nutrition support) Inpatient Provider NR Enteral	Common hospital diets	Weight or body composition changes
Zhu, 2019[200] (31464391) Asia Key Question 2, 3 Low	140 60 years 32% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes NRS-2002	Nutrition (500 kcal/d total of ONS (over 3 feedings) from discharge to 90 days + nutrition education) Outpatient Physician Oral	Nutrition education	Weight or body composition changes Adverse events Quality of life Functional status

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Zietarska, 2017[201] (29019951) Europe Key Question 2, 3 High	95 64 years 48% female Race NR	Gastrointestinal 32% Stage IV disease Chemotherapy alone Yes Multiple tools	Nutrition (high-energy, high-protein ONS, 250 ml/day x 3 mo.) Other Multiple providers Oral	Without nutritional support (ie, ONS)	Weight or body composition changes Changes in nutritional Status Adverse events Treatment tolerance Quality of life Symptoms Functional status

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NA = not available; NRS = nutritional risk screening; POD = post operative day; PN = parenteral nutrition; EPA = eicosapentaenoic acid; TPN = total parenteral nutrition; EN = enteral nutrition; ONS = oral nutritional supplement; BCAA = branched-chain amino acid

*For select studies only.

†Reports median age when mean is not available.

Multi-Component Interventions

Table E.6. Characteristics of included studies: use of multi-component interventions during cancer treatment (KQ2)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Abdollahi, 2019[202] (30945949) Other Key Question 2 Not conducted	150 46 years 100% female Race NR	Other % Stage IV disease NR Chemotherapy alone Yes Screening tool NR	Multi-modality (face to face nutritional education with dietary recommendation) Outpatient Dietitian/nutritionist Oral	Received a pamphlet	Adverse events
Demark-Wahnefried, 2008[203] (18501061) North America Key Question 2, 3 Not conducted	90 42 years 100% female Non-Hispanic White	Other 0% Stage IV disease Chemotherapy alone No Screening tool NR	Multi-modality (calcium rich diet with exercise) Outpatient Dietitian/nutritionist Oral	Calcium rich with exercise and high fruit and vegetable, low-fat diet	Weight or body composition changes Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Lin, 2017[204] (28658162) Asia Key Question 2 Not conducted	110 Age NR 36% female Asian	Gastrointestinal 44% Stage IV disease Chemotherapy alone No NRS-2002	Multi-modality (individual recipes plus enteral or parenteral nutrition) Multiple settings Nurse Other	Nutrition screening, nutritional guidance, diet mission, and arranged mealtimes	Weight or body composition changes
Poulsen, 2014[205] (24269077) Europe Key Question 2, 3 Not conducted	61 66 years 57% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies No NRS-2002	Multi-modality (nutritional counseling plus high-protein nutrition supplement) Outpatient Dietitian/nutritionist Oral	The control group was nutritionally instructed by the nurses with the possibility to call for a dietitian if needed	Weight or body composition changes Quality of life Symptoms
Qin, 2021[206] (34249995) Asia Key Question 2 Not conducted	60 54 years 100% female Race NR	Other (Ovarian) 12% Stage IV disease Chemotherapy No Other tool	Nutritional health education including designing healthy recipes and prevention for common nutritional problems along with ONS (250 ml (Ensure® three times a day) Setting NR Professional nutritionist Oral	Nutrition education	Changes in nutritional status
Silander, 2012[207] (21374756) Silander, 2013[208] (23169469) Europe Key Question 2, 3 Not conducted	134 62 years 32% female Race NR	Head & Neck 74% Stage IV disease Chemotherapy alone Yes Screening tool NR	Multi-modality (nutritional counseling plus percutaneous endoscopic gastrostomy feeding Outpatient Dietitian/nutritionist Enteral	Nutritional support according to clinical praxis, which could include nutritional advice and enteral tube feeding	Weight or body composition changes Changes in nutritional status Adverse events Survival Length of stay Quality of life Symptoms Functional status

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Skaarud, 2019[209] (31455897) Europe Key Question 2 Not conducted	117 43 years 38% female Race NR	Other % Stage IV disease NR Multiple therapies No Screening tool NR	Multi-modality (patients received routine hospital food and were encouraged to take energy-enriched and lactose-reduced snacks and oral supplements daily. A nasoenteric tube was inserted within 5 days after transplantation) Multiple settings Provider NR Other	Routine hospital procedure for nutritional support	Weight or body composition changes Survival
Song, 2017[210] (28943912) Asia Key Question 2, 3 Not conducted	86 56 years 48% female Race NR	Head & Neck % Stage IV disease NR Surgery alone No Other tool	Multi-modality (preoperative nutritional support therapy, postoperative nutritional therapy during hospitalization, and nutrition therapy outside the hospital) Multiple settings Multiple providers Other	Routine nutritional support therapy after surgery	Changes in nutritional status Adverse events Readmissions or emergency room visits Survival Length of stay Quality of life
Uster, 2013[211] (24103511) Europe Key Question 2, 3 Not conducted	58 65 years 21% female Race NR	Multiple Cancers % Stage IV disease NR Cancer Treatment Type NR Yes NRS-2002	Multi-modality (standardized individual nutritional therapy, including counseling by a dietitian, food fortification, and ONS if required) Outpatient Dietitian/nutritionist Oral	Standard care	Weight or body Composition changes Changes in nutritional Status Quality of life Functional status

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Xie, 2017[212] (28524705) Asia Key Question 2 Not conducted	144 55 years 41% female Asian	Gastrointestinal 10% Stage IV disease Multiple therapies No Screening Tool NR	Multi-modality (intensive individualized nutritional and educational interventions during the entire course of chemotherapy) Multiple settings Multiple providers Other	Basic nutrition care and health education during hospitalization	Weight or body composition changes Changes in nutritional status

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; ONS = oral nutritional supplement.
*For select studies only.
†Reports median age when mean is not available.

Risk of Bias and Outcome Assessment

Table E.7.1. Risk of bias assessment: use of dietary supplements during cancer treatment (KQ2)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
de Luis, 2004[81] (15138461)	Inpatient	Medium	High	X	X	X	X	High
de Luis, 2005[82] (15802904)	12 weeks	Medium	High	X	X	X	X	High
De Luis 2007[83] (16929239)	Inpatient	Medium	Medium	Medium	Low	Low	Low (0)	Medium
De Luis 2008[84] (18700689)	3 mo.	Low	Medium	Medium	Low	Low	Low (0)	Medium
de Luis 2009[85] (19694342)	Inpatient	Medium	Low	Low	Medium	Low	Low (0)	Medium
De Luis, 2010[86] (21284343)	Inpatient	Medium	Low	Low	Medium	Low	Low (0)	Medium
de Luis, 2015[87] (25855918)	Inpatient	Medium	Low	Low	Low	High	Low (0)	High
Farreras 2005[88] (15681102)	Inpatient	Medium	Low	Low	Medium	Low	Low 9%	Medium
Golkhalkhali 2018[90] (28857425)	2 mo, 6 mo	Medium	Medium	Medium	Medium	Low	Low (attrition NR)	Medium

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Jiang Z, 2010[92] 20473991	8d postop	Low	Low	Medium	Low	Low	Low 1%	Low
Klek, 2005[93] (15906909)	Inpatient	Medium	High	X	X	X	X	High
Lobo 2006[94] (16777271)	11 wks; 4 mo mortality	Low	Low	Low	Low	Low	Medium 10%	Low
Lu, 2011[96] (213963072)	Inpatient	Medium	Medium	Medium	Medium	Low	Low	Medium
Matsuda, 2017[97] (28138734)	Inpatient, 28d	Medium	High	X	X	X	X	High
Miyata, 2017[98] (27644137)	Inpatient	Medium	Medium	Low	Medium	Low	Low	Medium
Pathak 2019[99] (31410338)	7 weeks	Low	Medium	Medium	Medium	Low	Low 7%	Medium
Pottel 2014[100] (25293388)	7 weeks	Low	Medium	Low	Low	Medium	Medium (17%)	Medium
Sun, L 2008[101] (18376691)	Inpatient	Medium	Low	Medium	Medium	Low	Low (0)	Medium
Takeshita 2009[102] (19285598)	2 weeks	Medium	Medium	Medium	Medium	Low	Low (0)	Medium
Wang, 2013[106] 24379010	Inpatient	Low	Low	Medium	Medium	Low	Low (0)	Low
Wang, 2017[105] (28927119)	Inpatient	Low	Low	Medium	Medium	Low	Low (0)	High
Wang, 2010[107] (21208095)	Inpatient	Low	Low	Low	High	Low	Low 4%	Medium
Wu, 2012[108] (23554777)	6 months	Low	Medium	High	Medium	Medium	Low (0)	High
Yang, 2022[109, 196] (35500316)	Inpatient, 30 d	Low	Medium	Low	Medium	Low	Low (2%)	Medium
Yeh, 2013[110] (23562359)	8 weeks	Low	Medium	High	Medium	Low	Low (0)	High
Zhu M, 2012[112] 22340541	Inpatient	Low	Low	Medium	Low	Low	Low 5%	Low

Note: X indicates domain not assessed due to previously determined high risk of bias.
Abbreviations: PMID = PubMed Identification Number; mo = months; wks = weeks; POD = postoperative day; KQ=Key Question

Table E.7.2. Outcomes assessment: use of dietary supplements during cancer treatment (low and medium ROB studies), KQ2

Author, Year, RoB Timing	N	Treatment	Control	Weight / Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/Emergency Room Visits	Survival	LOS	Treatment Tolerance	QoL	Symptoms	Functional Status
de Luis 2007[83] (16929239) Medium Inpatient	72	Postop arginine enhanced EN (17 g/day)	Postop standard EN	↔	NA	↑ fistula ↔ other AEs	NA	NA	↔	-	-	-	-
De Luis 2008[84] (18700689) Medium 3 mos	65	Postop oral omega 3 supplement with high ratio omega3 /omega6	Postop oral omega 3 supplement with low ratio omega3/ omega6	↔	NA	↔	NA	NA	NA	-	-	-	-
de Luis 2009[85] (19694342) Medium Inpatient	72	Postop arginine enhanced EN (20 g/day)	Postop standard EN	↔	NA	↑ Fistula ↔ other AEs	NA	NA	↑	-	-	-	-
De Luis, 2010[86] (21284343) Medium Postop day 10	115	Postop high arginine EN (20 g/day)	Postop medium arginine EN (12.3 g/day)	↔	NA	↑ Fistula ↔ other AEs	NA	NA	↔	-	-	-	-
Farreras 2005[88] (15681102) Medium Inpatient	66	Early postop IEN with arg., omega 3 FAs & RNA	EN	NA	NA	↑ any AE ↑ wound-related	NA	↔	↑	-	-	-	-
Golkhalkhali 2018 [90] (28857425) Medium 2mo, 6 mo	140	Probiotic (4 wks) + 2 g. omega 3 FAs (8 wks)	Placebo	↔ 2 mo ↔ 6 mo	NA	NA	NA	NA	NA	-	-	-	-
Jiang Z, 2010[92] 20473991 Low Inpatient	200	PN with soybean oil + fish oil POD 1-8	PN with soybean oil POD 1-8	↔	NA	↑ SIRS ↔ other	NA	NA	↑	-	-	-	-
Lobo 2006[94] (16777271) Low 11wks, 4 mo	120	IEN (J-tube) x 10-15d postop	Other EN x 10-15d postop	NA	NA	↔ infectious ↔ non-infectious ↔ J-tube	NA	↔	↔	-	-	-	-

Author, Year, RoB Timing	N	Treatment	Control	Weight / Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/Emergency Room Visits	Survival	LOS	Treatment Tolerance	QoL	Symptoms	Functional Status
Lu, 2011[96] (213963072) Medium Inpatient	50	Glutamine-enriched TPN x 7d postop.	Standard TPN x 7d psotop	NA	NA	↑ ↔ infectious AEs	NA	NA	NA	-	-	-	-
Miyata, 2017[98] (27644137) Medium Inpatient	61	Chemo ONS with FA's	Chemo Standard ONS	↔ Wt day 12 ↑ EPA levels day 8	NA	↑ Stomatitis ↔ other	NA	NA	NA	-	-	-	-
Pathak 2019[99] (31410338) Medium 7 weeks	60	10 gm oral glutamine 2 hr before chemo-radiation, 5d/wk x 7 wks	No glutamine x 7 wks	↑	NA	↑ oral mucositis ↑ dysphagia	↑	NA	NA	-	-	-	-
Pottel 2014[100] (25293388) Medium 4 weeks	91	7.5 mL Echium oil 2x/day during radio(chemo)therapy	7.5 mL Sunflower oil 2x/day during radio(chemo) therapy	↑ FFM ↔ other	↔	↔	NA	NA	NA	-	-	-	-
Sun, L 2008[101] (18376691) Medium Inpatient	64	BCAA-enriched (30%) TPN postop	Standard TPN (24% BCAA)	↔ POD 7	NA	↑ any AE ↔ individual AEs	NA	↔	NA	-	-	-	-
Takeshita 2009[102] (19285598) Medium 2 weeks	56	BCAA snack x 15 d (1d preop+14d) post chemo-embolization	"control group"	↔	NA	NA	NA	↔	↔	-	-	-	-
Wang, 2010[107] (21208095) Medium Inpatient	229	Triglyceride & protein-enriched EN	NA	NA	NA	↔ infections	NA	NA	↑	-	-	-	-
Wang, 2013[106] 24379010 Low Inpatient	94	EN + PN with olive oil-based lipids ≥ 7 d postop	EN + PN with triglycerides ≥ 7 d postop	NA	NA	↔ infectious ↔ any	NA	↔	↔ ↔ ICU	-	-	-	-
Yang, 2022[109] (35500316) Medium Inpatient, 30 d	120	EN & PN with n-3 fatty acids POD 1-5	EN & PN	NA	NA	↑postoperative complications	↔ readmissions	↔	↔	-	-	-	-

Author, Year, RoB Timing	N	Treatment	Control	Weight / Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/Emergency Room Visits	Survival	LOS	Treatment Tolerance	QoL	Symptoms	Functional Status
Zhu M, 2012[112] 22340541 Low Inpatient	57	0.2 g/kg/d fish oil + 1 g/kg/d soybean oil in TPN x 7d postop	TPN x 7d postop	NA	NA	↔ infectious ↑ SIRS ↔ serious AEs (none)	NA	NA	↑	-	-	-	-

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; BMI: body mass index; FFM: fat free mass; AE: adverse events; LOS: length of stay; QOL: quality of life; PN: parenteral nutrition; IEN=immunoenteral nutrition; UTD: unable to determine; abd. sx = abdominal symptoms; EN: enteral nutrition: TPN: total parenteral nutrition: ICU: intensive care unit: SIRS: systemic inflammatory response syndrome; d: day: BCAA=Branched chain amino acid; KQ= Key Question; NA=not assessed.
↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer AEs, shorter LOS than comparison group).
↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more AEs, longer LOS).
↔: No statistically significant difference between groups.

Table E.8.1, Risk of bias assessment: route or timing of nutritional interventions during cancer treatment (KQ2)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Berkelmans 2020[122] (31090563)	Inpatient, 30 d, 3 mo.	Low	Medium	Medium	Medium	Low	Medium 11%	Medium
Boelens, 2014[123] (24169163)	Inpatient	Low	High	X	X	X	X	High
Bozzetti, 2001[124] (11705560)	Inpatient	Low	Low	Medium	Low	Low	Low 2%	Low
Braga, 2001[125] (11246300)	Inpatient	Low	Medium	Medium	Low	Medium	Low 3%	Medium
Dag, 2011[126] (22189721)	Inpatient	Low	High	X	X	X	X	High
Feo 2004[127] (15144242)	Inpatient	Low	Medium	Medium	Low	Low	Low (0)	Medium
Gao, 2019[128] (30941970)	Inpatient	Medium	High	X	X	X	X	High
Huang, 2015[129] (1594390)	Inpatient	Medium	High	X	X	X	X	High
Hyltander, 2005[130] (15880316)	1 year	Low	High	X	X	X	X	High
Kita, 2021[131] (33526287)	Inpatient	High	X	X	X	X	X	High
Kurbanalievich, 2020[132] (2005564409)	Inpatient	Medium	Medium	Medium	Medium	Low	Low (0)	Medium

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Li, 2015[133] (26011337)	Inpatient	Medium	Medium	High	X	X	X	High
Ma, 2020[136] (33362392)	Inpatient	Low	Medium	Medium	Medium	Medium	Low 3%	Medium
Luo, 2018[135] (28666095)	Inpatient, 20 months	Low	Medium	High	X	X	X	High
Mahmoodzadeh, 2015[137] (24875466)	Inpatient	Medium	High	X	X	X	X	High
Perinel, 2016[139] (27429039)	Inpatient, 30d	Low	Medium	Medium	High	X	X	High
Sun, 2018[145] (28549015)	Inpatient, readmissions, HRQoL 24 wk	Low	Medium	Medium	Medium	Low	Low (0)	Medium
Tao 2020[146] (31512101)	Inpatient, 1 mo., 3 mo.	Medium	Medium	Medium	Low	Medium	Low (0)	Medium
van Barneveld, 2016[147] (26937858)	Inpatient	Low	High	X	X	X	X	High
Wang 2019[148] (931239762)	30 days	Low	Medium	Medium	Medium	Low	Low 1%	Medium
Wang, 2018[149] (29896256)	Inpatient	Medium	Medium	Medium	Medium	Medium	Low (0)	Medium
Xiao-Bo 2014[150] (924504222)	Inpatient	Medium	Medium	Medium	Medium	Low	Low (0)	Medium
Xu, 2020[151] PMID NA	Inpatient	Medium	Medium	High	X	X	X	High
Zhang, 2019[152] (31551229)	Inpatient	Low	High	X	X	X	X	High

Note: X indicates domain not assessed due to previously determined high risk of bias.
Abbreviations: PMID = PubMed Identification Number; HRQoL = health related quality of life; NA = not available; mo = months; wk = weeks; KQ= Key Question.

Table E.8.2. Outcomes assessment: route or timing of nutritional interventions during cancer treatment (low and medium ROB studies), KQ2

Author, Year, PMID RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QoL	Symptoms	Functional Status
Berkelmans 2020[122] (31090563) Medium Inpatient, 30d; 90d (mortality)	148	Postop early oral feeding (POD1)	tube feeding x 5d (while NPO)	↔ 1 mo ↔ 3 mo	↓ kcal	↔ pneumonia ↑ chyle leak ↔ other AEs	↔ readmit	↔ 90d	↔	-	-	-	-

Author, Year, PMID RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QoL	Symptoms	Functional Status
Bozzetti, 2001[124] (11705560) Low Inpatient	317	Postop EN in malnourished	Postop PN in malnourished	NA	NA	↑ any on list ↑ infectious	NA	UTD	↑	-	-	-	-
Braga, 2001[125] (11246300) Medium Inpatient	257	Postop TPN	Postop early EN	NA	NA	↔ any ↔ infectious ↔ noninfect.	NA	↔	↔	-	-	-	-
Feo 2004[127] (15144242) Medium Inpatient	100	No NG tube, clear liq POD 1, advance to soft diet	NG tube to flatus, liquid diet to soft diet	NA	NA	↔ complications	NA	↔ (0 death)	↔	-	-	-	-
Kurbanalievich, 2020[132] PMID NA Medium Inpatient	80	EN from POD 2	Isolated parenteral nutrition from POD 1	↔	NA	NA	NA	NA	NA	-	-	-	-
Ma, 2020[136] (33362392) Medium Inpatient	60	Postop early EN + PN	Postop TPN	NA	NA	↔ SSI ↔ bile leak	NA	NA	↑	-	-	-	-
Sun, 2018[145] (28549015) Medium Inpatient, 6m	280	Early oral feeding with liquid foods on post-op day 1	Nasoenteral nutrition post-op	↔	NA	↔ complications	NA	↔	↑	-	-	-	-
Tao 2020[146] (31512101) Medium Inpatient, 3mo	120	Postop EN via J-tube	Postop EN via NG tube	↑	NA	↔ overall complications ↓ intestinal obstruction	NA	↔ DFS, OS	NA	-	-	-	-
Wang 2019[148] (31239762) Medium Inpatient	100	Early oral feeding postop	Delayed oral feeding postop	NA	NA	↔ complications		NA	↑	-	-	-	-

Author, Year, PMID RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QoL	Symptoms	Functional Status
Wang, 2018[149] (29896256) Medium Inpatient	129	Postop EN	Postop TPN	↑ POD4 ↔ POD8	NA	↑complications	NA	NA	↑	-	-	-	-
Xiao-Bo 2014[150] (24504222)	120	Enteral nutrition, 1000 mL, 4.18 kJ/mL	Parenteral nutrition mixture	NA	NA	↑ bacterial, fungal infection	NA	NA	↔	-	-	-	-

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; NA = not available; BMI: body mass index; FFM: fat free mass; AE: adverse events; LOS: length of stay; QOL: quality of life; PRO: patient reported outcome; POD: post operative day: DFS: disease free survival: OS: overall survival: EN: enteral nutrition: TPN: total parenteral nutrition: NG: nasogastric; sx = abdominal symptoms; SSI: surgical site infection; UTD: unable to determine; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire; SF-36 = short-form health survey; -: Not applicable.

Table E.9.1. Risk of bias assessment: use of nutrition support including oral nutrition supplements during cancer treatment (KQ2)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Barlow, 2011[155] (21601319)	Inpatient, 6 & 12 wks.	Low	Medium	Low	Low	Low	Low (0)	Medium
Chen T, 2021[159] (34237976)	1 month post-hospital discharge after surgery	Low	High	X	X	X	X	High
Chu, 2018[160] (622367981)	Inpatient	Low	Medium	Medium	Medium	Low	Low (0)	Medium
Gavazzi, 2016[163] (27391922)	6 months	Low	High	X	X	X	X	High
Imamura, 2016[165] (27084538) Kimura, 2019[166] (31788653)	8 weeks	Low	High	X	X	X	X	High
Jin, 2018[168] (30205371)	Inpatient	Medium	Medium	High	X	X	X	High
Katada, 2021[170] (33009977)	2 months	Low	High	X	X	X	X	High
Klek, 2011[174] (21820770) Klek, 2014[175] (24178182)	Inpatient	Low	Medium	Medium	Low	Low	Low 4%	Medium

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Klek, 2008[171] (18571296) Klek, 2011[172] (21074910) Klek, 2017[173] (28336107)	Inpatient	Low	Low	Low	Medium	Low	Low 7%	Low
Li C, 2020[177] (2003914110)	3 yrs (survival)	Medium	Medium	Medium	Medium	Low	Low	Medium
Li, 2015[176] (26125924)	Inpatient	Low	High	X	X	X	X	High
Lyu, 2022[178] (35280748)	After treatment completion (2-3 cycles) & up to 4 yrs	Low	Medium	High	Medium	Low	Medium (19%)	High
Meng, 2021[180] (32563598) Tan 2021[181] (32563599)	3 mo	Low	Low	Medium	Medium	Low	Low 5%	Low
Miyazaki 2021[182] (33835329)	1, 3, 6, 12 mo.	Low	Low	Medium	Medium	Low	Low 12%	Medium
Nie, 2021[183] (35035754)	NR	Medium	Medium	High	Medium	Low	Low (0%)	High
Okabayashi, 2011[185] (20852905)	1 year	Medium	Medium	High	X	X	X	High
Ohkura, 2019[184] (30169605)	Inpatient, 6 m	Low	High	High	X	X	X	High
Scislo, 2018[189] (29533110)	Inpatient, 1 yr	Low	High	X	X	X	X	High
Shimizu, 2018[190] (29721714)	Inpatient	Low	Medium	High	X	X	X	High
Sim, 2022[191] (35225460)	Weeks 0, 4, 8	Medium	Medium	High	Medium	Low	High (31%)	High
Wang J, 2022[193] (35126900)	Inpatient	Low	High	X	X	X	X	High
Wu, 2017[194] (27208039)	Inpatient; 90 d QOL	Low	Medium	Medium	Medium	Low	Medium 13%	Medium
Xie, 2021[195] (334988183)	Inpatient, 1 mo., 3 mo., 6 mo.	Low	Medium	Medium	Low	Low	Medium (14%)	Medium
Yang, 2020[196] (32833549)	3 days	Low	Medium	High	X	X	X	High
Yao 2019[197] (31646824)	Inpatient	Low	Medium	Medium	Medium	Low	Low (0)	Medium

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Zhu 2019[200] (31464391)	30, 60, 90 days	Low	Low	Medium	Midium	Low	Medium 19%	Low
Zietarska, 2017[201] (29019951)	12 weeks	Low	Low	Medium	Low	Medium	High (24%)	High

Note: X indicated domain not assessed due to previously determined high risk of bias.
Abbreviations: PMID = PubMed Identification Number; d = days; wks = weeks; mo = months; yr = years; KQ= Key Question.

Table E.9.2. Outcomes assessment: use of nutrition support including oral nutrition supplements during cancer treatment (low and medium ROB studies), KQ2

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms	Functional Status
Barlow, 2011[155] (21601319) Medium Inpatient, 12w	121	Early EN within 12h of surgery (20 kcal/h)	IV hydration	NA	NA	↑ infective complications	↔	UTD	↑	-	-	-	-
Chu, 2018[160] (62236798 1) Medium Inpatient	98	Postop EN+PN	Postop routine PN	NA	↑	↑ complications	NA	NA	↑	-	-	-	-
Klek, 2011[174] (21820770) Klek, 2014[175] (24178182) Medium Inpatient	167	1. IMEN; 2. SPN 3. IMPN 24h after surgery for at least 7d	Standard EN	NA	NA	↔ Infectious complications	NA	↔ 30d	↔	-	-	-	-
Klek, 2008[171] (18571296) Klek, 2011[172] (21074910) Klek, 2017[173] (28336107) Low Inpatient	196	IMEN	Standard EN	NA	NA	↔ complications	NA	↔	NA	-	-	-	-

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms	Functional Status
Li C, 2020[177] (PMID NA) Medium 3yrs	78	Post-chemo early IEN	Conventional nutrition support	NA	NA	↑	NA	↑ 3 yr	NA	-	-	-	-
Meng, 2021[180] (32563598) Tan 2021[181] (32563599) Low	353	Oral nutritional supplements with dietary advice	Dietary advice alone	↑	NA	NA	NA	NA	NA	-	-	-	-
Miyazaki 2021[182] (33835329) Medium 1 yr	1003	Postop 400 ml ONS x 3 mo. (+ regular diet)	No ONS postop (+ regular diet)	↑ 3 mo. ↑ 6 mo. ↔ 1 yr.	NA	↔ any surgical AE	NA	NA	NA	-	-	-	-
Wu, 2017[194] (27208039) Medium Inpatient	80	Post-op EN+PN via NJT/ j-tube	Post-op EN via NJT/ j-tube	↑ FFM ↑ BW ↔ FM	NA	↔ postoperative complications	NA	NA	↔	-	-	-	-
Xie, 2021[195] (33498818 3) Medium Inpatient, 1 mo., 3 mo., 6 mo.	77	300 mL oral nutritional supplement in addition to standard diet	Regular diet alone	↑body weight loss	NA	↔ Anastomotic leak, pneumonia, pleural effusion, atelectasis, 41espirator failure, myocardial arrhythmia, heart failure, any complication	↔ readmissions	↔	↔ Hospital, ICU stay	-	-	-	-

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms	Functional Status
Yao, 2019[197] (31646824) Medium Inpatient	114	Early EN postop via NG tube	Routine oral nutrition support	NA	NA	↑ total count	NA	NA	↑	-	-	-	-
Zhu, 2019[200] (31464391) Low 30-90 days	140	500 kcal ONS 3x/d x 90d + dietary advice from doctor at hospital discharge	Dietary advice from doctor at hospital discharge	↔ 30d weight/ BMI ↑ 60d weight/ BMI ↑ 90d weight/ BMI ↔ FFM	NA	↔ (none)	NA	NA	NA	-	-	-	-

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; NA = not available BMI: body mass index; FFM: fat free mass; AE: adverse events; LOS: length of stay; QOL: quality of life; PRO: patient reported outcome; d; day: EN: enteral nutrition: NG: nasogastric: ONS: oral nutritional supplement: PN: parenteral nutrition: IMEN: immunomodulating enteral nutrition: SPN: standard parenteral nutrition: IMPN: immunomodulating parenteral nutrition: IEN: immunomodulating enteral nutrition: EQ-5D: EuroQol-5D: UTD: unable to determine; KQ = Key Question; FM = fat mass; NJT = nasojejunal tube; NA=not assessed.

-: Not applicable.

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer Aes, shorter LOS than comparison group).

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more Aes, longer LOS).

↔: No statistically significant difference between groups.

Appendix F. Evidence Tables for Chapter 8

Nutritional Counseling

Table F.1. Characteristics of included studies: use of nutritional counseling for cancer and treatment related symptoms (KQ3)

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Britton, 2019[64] (30296472) Other Key Question 2, 3 Not conducted	307 58 years 21% female Other	Head & Neck 65% Stage IV disease Radiation alone No Screening tool NR	Counseling only (Eating As Treatment (EAT) dietary advice) Outpatient Dietitian/nutritionist Not applicable	Treatment as usual	Weight or body composition changes Changes in nutritional status Treatment tolerance Quality of life
Forslund, 2020[65] (31758324) Europe Key Question 2, 3 Not conducted	180 67 years 0% female Race NR	Other 4% Stage IV disease Radiation alone No Screening tool NR	Counseling only (advised to increase soluble fiber and decrease lactose in diet) Outpatient Dietitian/nutritionist Not applicable	Standard care	Adverse events Quality of life
Isenring, 2004[66] (15226773) Other Key Question 2, 3 Not conducted	60 62 years 15% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies No Other tool	Counseling only (intensive nutritional counseling for up to 3 months) Outpatient Dietitian/nutritionist Not applicable	Less intensive diet education by nurses	Weight or body composition changes Changes in nutritional Status Quality of life Functional status
Movahed, 2020[68] PMID NA Other Key Question 2, 3 Not conducted	100 67 years 49% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Other tool	Counseling only (individualized dietary plan and nutrition education) Setting NR Other provider Not applicable	General dietary advice at the beginning of the treatment	Weight or body composition changes Changes in nutritional status Symptoms Functional status

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Najafi, 2019[213] (30449171) Asia Key Question 3 Not conducted	150 58 years 100% female Race NR	Other % Stage IV disease NR Chemotherapy alone No Screening tool NR	Counseling only (Personalized diet and nutrition education before each chemotherapy session) Setting NR Dietitian/nutritionist Not applicable	Usual diet + regular chemotherapy drug regimen with no pamphlet, nutritional education, or dietary intervention	Quality of life Symptoms Functional status
Pettersson, 2012[70] (22633817) Region NR Key Question 2, 3 Not conducted	130 66 years 0% female Race NR	Other % Stage IV disease NR Radiation alone No Other tool	Counseling only (advised to increase soluble fiber and decrease lactose in diet) Setting NR Dietitian/nutritionist Not applicable	Standard care (advised to continue normal diet)	Adverse events Symptoms Functional status
Qiu, 2020[71] (31526964) Asia Key Question 2, 3 Not conducted	85 67 years 36% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Multiple tools	Counseling only (whole-course nutrition management) Inpatient Multiple providers Not applicable	The control group was treated with general nutritional supplementation	Weight or body composition changes Adverse events Length of stay Quality of life Symptoms
Ravasco, 2012[72] (23134880) Europe Key Question 2, 3 Not conducted	89 64 years 46% female Race NR	Gastrointestinal % Stage IV disease NR Radiation alone No Other tool	Counseling only (individualized nutritional counseling and education about regular foods weekly for 6 weeks) Outpatient Provider NR Not applicable	Group 2: dietary supplements and consumed usual diet of regular foods Group 3: consumed usual diet of regular foods	Weight or body composition changes Changes in nutritional status Adverse events Survival Quality of life Symptoms
Regueme, 2021[73] (32435967) Europe Key Question 2, 3 Not conducted	283 77 years 50% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone Yes Other tool	Counseling only (usual care + support to increase intake) Outpatient Dietitian/nutritionist Not applicable	Usual care: received nutritional care routinely used in the cancer treatment setting	Weight or body composition changes Quality of life Symptoms Functional status

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Um, 2014[75] (24906838) Asia Key Questions 2, 3 Not conducted	87 60 years 36% female Race NR	Multiple cancers % Stage IV disease NR Radiation alone Yes Other tool	Counseling only (at least 3 sessions of individualized dietary counseling concurrent with radiation) Outpatient Dietitian/nutritionist Not applicable	One routine 20-min education session by a dietitian within 4 days of starting RT	Weight or body composition changes Changes in nutritional status Survival Quality of life
van der Werf, 2020[76] (32037284) Europe Key Questions 2, 3 Not conducted	107 65 years 37% Race NR	Gastrointestinal 100% Stage IV disease Chemotherapy alone No Screening tool NR	Counseling only (individualized nutritional counseling) Outpatient Dietitian/nutritionist Not applicable	Usual care	Weight or body composition changes Survival Treatment tolerance Quality of life Functional status
Zhang Z, 2022[77] (34984549) Asia Key Question 2, 3 Not conducted	468 60 years 42% female Race NR	Multiple Cancers 37% Stage IV disease Radiation Therapy No Multiple tools	Nutrition education (guideline-based nutrition education counseling that was tailored and dynamic) Inpatient Nurse Not applicable	No nutrition education	Changes in nutritional status Treatment tolerance

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; RT = radiotherapy.
*For select studies only.
†Reports median age when mean is not available.

Dietary Supplements

Table F.2. Characteristics of included studies: use of dietary supplements for cancer and treatment related symptoms (KQ3)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Cereda, 2019[22] (31568698) Europe Key Question 1 & 2, 3 Not conducted	166 65 years 40% female Race NR	Multiple cancers 81% Stage IV disease Chemotherapy alone Yes Other metric	Single Supplement (WPI supplementation) Outpatient Dietitian/nutritionist Oral	Nutritional counseling alone	Weight of body composition changes Treatment tolerance Quality of life
Dechaphunkul, 2022[1] 35007812 Asia Key Question 1, 3 Not conducted	110 52 years 21% female Race NR	Head & Neck 76% Stage IV disease Chemotherapy No Other (Nutritional Risk Index)	Immunonutrition with FA's, arginine, fiber & nucleotides, 3x/day for 5 days before each chemotherapy session. Outpatient Dietitian/nutritionist Oral	Standard enteral formula, 3x/day for 5 days before each chemotherapy	Weight or body composition changes Symptoms Survival
Fietkau, 2013[89] (23765693) Europe Key Question 2, 3 Not conducted	111 56 years 16% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies No Other tool	Single Supplement (Disease-specific enteral formula (Supportan)) Outpatient Physician Enteral	500 mL of the enteral standard nutrition Fresubin energy fibre	Weight or body composition changes Changes in nutritional Status Quality of life Functional status
Golkhalkhali, 2018[90] (28857425) Asia Key Question 2, 3 Medium	140 Age NR % female NR Asian	Gastrointestinal % Stage IV disease NR Chemotherapy alone No Screening tool NR	Single Supplement (Microbial cell prep and omega-3 fatty acids) Inpatient Provider NR Oral	Placebo	Weight or body composition changes Quality of life Symptoms
Iwase, 2016[91] (26105516) Asia Key Question 2, 3 Not conducted	59 Age NR 100% female Race NR	Other 14% Stage IV disease Chemotherapy alone No Screening tool NR	Supplements (Amino acid jelly (Inner Power) oral diet supplement) Setting NR Provider NR Oral	Regular care	Adverse events Quality of life Symptoms

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Serrano, 2022[30] (35606184) Canada Key Question 1 & 2, 3 Medium	71 65 years 41% female Race NR	Gastrointestinal 69% Stage IV disease Surgery No MUST	Supplements (protein supplementation rich in arginine and omega-6 and carbohydrate loading) Other Nurse Oral	One placebo to each supplement	Adverse events Readmissions or Emergency room visits Survival Length of Stay Quality of life
Tanca, 2009[103] PMID NA Europe Key Question 2, 3 Not conducted	475 62 years 40% female Race NR	Multiple cancers 95% Stage IV disease Cancer treatment type NR Yes Multiple tools	Supplements (5 treatment groups: 1) Progestational agent, 2) EPA, 3) L-carnitine, 4) Thalidomide, 5) Progestational agent plus pharmacologic nutritional support and L-carnitine and thalidomide) Other Provider NR Oral	No placebo or control	Weight or body composition changes Quality of life Symptoms Functional status
Tsuchiya, 2016[34] (27306219) Asia Key Question 1 & 2, 3 High	70 63 years 40% female Race NR	Gastrointestinal % Stage IV disease NR Multiple therapies No Screening Tool NR	Supplements (added amino acids) Outpatient Provider NR Oral	No supplement	Adverse events Treatment tolerance
Wang, 2017[105] (28927119) Asia Key Question 2, 3 High	94 59 years 37% female Race NR	Gastrointestinal 100% Stage IV disease Multiple therapies No Screening tool NR	Single Supplements (glutamine enriched nutritional support) Inpatient Provider NR Parenteral	Basic nutritional support	Adverse events Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Wang, 2010[107] (21208095) Asia Key Question 2, 3 Medium	229 56 years 36% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Supplements (EN enriched with medium-chain triglycerides and protein) Inpatient Multiple providers Enteral	Isocaloric EN for ≥5 days started within 48-72 h post-surgery	Adverse events Length of stay Symptoms

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NA = not available; EN = enteral nutrition; WPI = whey protein isolate;
*For select studies only.
†Reports median age when mean is not available.

Special Diets

Table F.3. Characteristics of included studies: use of special diets for cancer and treatment related symptoms (KQ3)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Ansari, 2016[214] (27644633) Asia Key Question 3 Not conducted	100+ 49 years 100% female Race NR	Other % Stage IV disease NR Chemotherapy alone No Screening tool NR	Single Supplement (Ginger capsules) Outpatient Other Oral	Placebo, 2 capsules every 12 hours for 3 days	Symptoms
Gardner, 2008[113] (18955453) North America Key Question 2, 3 Not conducted	153 64 years % female NR Race NR	Other % Stage IV disease NR Chemotherapy alone No Screening tool NR	Special Diets (diet with raw fruits and vegetables) Inpatient Provider NR Oral	Diet without raw fruits & vegetables	Weight or body composition changes Adverse events Survival Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Ingersoll, 2010[114] (20189927) North America Key Question 2, 3 Not conducted	77 54 years 81% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone No Screening tool NR	Special Diets (standard medical CINV management + grape juice) Outpatient Provider NR Oral	Standard medical CINV management	Adverse events Quality of life Symptoms
Jatoi, 2016[115] (27039205) North America Key Question 2, 3 Not conducted	118 Age NR 52% female Race NR	Other 100% Stage IV disease Multiple therapies No Screening tool NR	Special Diets (white wine twice daily) Outpatient Provider NR Oral	Nutritional supplement like boost or ensure	Adverse events Quality of life Functional status
Khodabakhshi, 2020[116] (314996287) Khodabakhshi, 2020[117] (32828130) Other Key Question 2, 3 Not conducted	80 Age NR 100% female Race NR	Other 26% Stage IV disease Chemotherapy alone No Screening tool NR	Special Diets (ketogenic) Outpatient Dietitian/nutritionist Oral	Standard diet	Weight or body composition changes Quality of life
Lugtenberg, 2021[118] (33179154) Europe Key Question 2, 3 Not conducted	129 50 years 100% female Race NR	Other % Stage IV disease NR Chemotherapy alone No Screening tool NR	Special Diets (calorie content declined for 3 days before and the day of treatment) Setting NR Physician Other	Regular diet	Weight or body composition changes Quality of life Symptoms Functional status
Miyakawa, 2019[119] (30554216) Asia Key Question 2, 3 Not conducted	100 71 years 66% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Special Diets (rice porridge) Inpatient Provider NR Oral	Liquid diet with gradual transition to solid food	Length of stay Quality of life Symptoms
Vafa, 2020[215] (32898787) Asia Key Question 3, 4 Not conducted	135 53 years 100% female Race NR	Other 0% Stage IV disease Multiple therapies No Screening tool NR	Special Diets (Calorie restricted diet + CFU symbiotic supplement) Outpatient Provider NR Oral	Calorie-restricted diet + placebo	Weight of body composition changes Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Voss, 2020[120] (32619561) Europe Key Question 2, 3 Not conducted	50 57 years % female NR Race NR	Other % Stage IV disease NR Radiation alone No Screening tool NR	Special Diets (3 days of ketogenic diet, 3 days of intermittent fasting, then 3 days of ketogenic diet) Outpatient Dietitian/nutritionist Oral	Calorically unrestricted diet	Survival Symptoms
Wedlake, 2012[121] (1605807) Europe Key Question 2, 3 Not conducted	100+ 65 years 32% female Race NR	Multiple cancers % Stage IV disease NR Radiation alone No Screening tool NR	Special Diets (Low fat and moderate fat intake) Outpatient Provider NR Oral	Normal fat (LCT - 40% of total energy)	Weight or body composition changes Quality of life Symptoms Functional status

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; CINV = hemotherapy-induced nausea and vomiting; LCT = long chain triglycerides.

*For select studies only.

†Reports median age when mean is not available.

Route or Timing of Nutritional Interventions

Table F.4. Characteristics of included studies: route or timing of nutritional interventions for cancer and treatment related symptoms (KQ3)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Brown, 2017[38] (28797454) Other Key Question 1 & 2, 3 Not conducted	131 60 years 12% female Race NR	Head & Neck 31% Stage IV disease Multiple therapies Limited to Malnourished NR Screening tool NR	Nutrition therapy (early feeding intervention via prophylactic gastrostomy tube) Multiple settings Dietitian/nutritionist Enteral	Usual care which commenced feeding when clinically indicated	Weight or body composition changes Changes in nutritional status Readmissions or emergency room visits Length of stay Treatment tolerance Quality of life
Feo, 2004[127] (15144242) Europe Key Question 2, 3 Not conducted	100 68 years % female NR Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutritiontherapy (clear oral liquids) Inpatient Provider NR Oral	Fasting until passage of flatus then NG diet	Adverse events Length of stay Quality of life
Mudge, 2018[43] (1596002) Other Key Question 1 & 2, 3 Not conducted	278 64 years 19% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Other tool	Nutrition therapy (immunonutrition (pre-, peri-, and post-op)) Inpatient Physician Other	Perioperative standard nutrition	Adverse events Survival Length of stay Quality of life
Roberts, 2003[140] (13130320) North America Key Question 2, 3 Not conducted	55 44 years 100% female Race NR	Other 58% Stage IV disease Multiple therapies No Multiple tools	Nutrition therapy (TPN) Inpatient Provider NR Parenteral	Oral diet post-surgery with IV fluids	Weight or body composition changes Adverse events Length of stay Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Sadasivan, 2012[142] (22973911) Asia Key Question 2, 3 Not conducted	100 Age NR % female NR Race NR	Head & Neck 50% Stage IV disease Multiple therapies No Screening tool NR	Nutrition therapy (percutaneous endoscopic gastrostomy) Setting NR Multiple providers Enteral	Nasogastric tube administration	Weight or body composition changes Adverse events Treatment tolerance
Sun, 2018[145] (28549015) Asia Key Question 2, 3 Not conducted	280 63 years 30% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No NRS-2002	Nutrition therapy (early oral feeding starting on POD 1) Inpatient Multiple providers Oral	Late Oral Feeding starting on POD 7	Adverse events Readmissions or emergency room visits Survival Length of stay Quality of life Symptoms
Tao, 2020[146] (31512101) Asia Key Question 2, 3 Not conducted	120 64 years 52% female Race NR	Gastrointestinal 11% Stage IV disease Surgery alone No Screening tool NR	Nutrition therapy (jejunostomy feeding starting on POD 1 until 3 wks past discharge) Inpatient Provider NR Enteral	Nasogastric feeding starting on POD 1 until discharge	Weight or body composition changes Changes in nutritional status Adverse events Survival Length of stay Quality of life
Wong TX, 2022[44] (35276977) Asia Key Question 1 & 2, 3 Not conducted	91 60 years 76% female Race NR	Multiple Cancers % Stage IV disease NR Surgery Yes Screening tool NR	Group SS: ONS (milk-based formula fortified with micronutrients)for 5 to 14 days preoperatively and postoperatively until discharge Group SS-E: ONS for 5 to 14 days pre-operatively and for 90-days post-discharge Multiple settings Provider NR Oral	ONS postoperatively until discharge	Weight or body composition changes Functional status

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; TPN = total parenteral nutrition; NG = nasogastric; POD = post-operative day; NRS = nutritional risk screening.
*For select studies only.
†Reports median age when mean is not available.

Nutrition Support Including Oral Nutrition Supplements

Table F.5. Characteristics of included studies: use of nutrition support including oral nutrition support for cancer and treatment related symptoms (KQ3)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Baker, 2015[154] (25827292) Other Key Question 2, 3 Not conducted	109 63 years 100% female Race NR	Other 10% Stage IV diseaseMultiple therapies Yes Other tool	Nutrition (intraoperative nasojejunal tube placement and enteral feeding until adequate oral intake could be maintained) Inpatient Multiple providers Enteral	Postoperative diet as tolerated	Adverse events Length of stay Quality of life
Bouleuc, 2020[156] (32212354) Europe Key Question 2, 3 Not conducted	148 66 years 55% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies Yes Screening tool NR	Nutrition (parenteral nutrition was administered by central venous route using industrial ternary preparations and systematic daily addition of polyvitamins, trace elements, and electrolytes (sodium, potassium, vitamin K, magnesium, phosphorus), adapted as required) Inpatient Dietitian/nutritionist Parenteral	Oral feeding	Weight or body composition changes Adverse events Survival Quality of life

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Cereda, 2018[157] (29111172) Europe Key Question 2, 3 Not conducted	159 65 years 28% female Race NR	Head & Neck 29% Stage IV disease Multiple therapies No Screening tool NR	Nutrition (2 bottles/day 250 mL of a ready-to-use energy-dense, high-protein, omega-3 enriched oral formula plus counseling) Outpatient Dietitian/nutritionist Oral	Counseling only	Weight or body composition changes Treatment tolerance Quality of life
Chen T, 2021[159] (34237976) Asia Key Question 2, 3 High	106 68 years 21% female Race NR	Gastrointestinal 0% Stage IV Surgery No NRS-2002	Post-hospital enteral nutritional emulsion via J-tube: 200-500 ml x 3-6x/day Outpatient (Home) Patient-delivered but directed by doctor, nurse & nutritionist J-tube x 1 month Enteral	Post-hospital gradual transition to soft to regular diet after 1 month (J tube in place x 1 mo, not used at home)	Weight or body composition changes Changes in nutritional status Symptoms
Chen X, 2021[8] (33752148) Asia Key Question 1, 3 Medium	139 59 years 38% female Race NR	Gastrointestinal 0% Stage IV Surgery (post-chemo-radiotherapy) No Screening Tool NR	Oral Nutrition (1000 ml of 10% glucose solution 10 hr. before surgery + 500 ml of same 2-3 hr. before surgery) Setting NR Provider NR Oral	500 ml of 10% glucose solution 2-3 hr. before surgery	Adverse events Length of stay Symptoms Readmissions or Emergency room visits
Faccio, 2021[162] (32363940) Other Key Question 2, 3 Not conducted	85 59 years 60% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone No Screening tool NR	Nutrition (nutritional supplement with counseling) Outpatient Dietitian/nutritionist Oral	Nutritional counseling alone	Weight or body composition changes Adverse events Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Feng, 2022[48] (34362624) Asia Key Question 1 & 2, 3 Low	126 70 years 37% female Race NR	Gastrointestinal % Stage IV NR Surgery No Screening tool NR	Preoperative oral CHO 200 ml. 2-3 hr. before surgery & postoperative early oral feeding (POD1=special clear liquid but no TPN; POD2=normal diet) Hospital inpatient Provider NR Oral	Fasted pre-surgery (> 8 hrs.) + TPN x 24 hr. post-surgery; advance diet as tolerated Hospital inpatient Provider NR Oral & TPN	Adverse events Readmissions or Emergency room visits Symptoms
Gavazzi, 2016[163] (27391922) Europe Key Question 2, 3 High	79 Age NR 38% female Race NR	Gastrointestinal 0% Stage IV disease Multiple therapies Yes NRS-2002	Nutrition (home enteral nutrition) Inpatient Multiple providers Enteral	Specific nutritional indications including total energy and protein requirements were provided	Weight or body composition changes Treatment tolerance Quality of life Functional Status
He F, 2022[10] (35406085) Asia Key Question 1, 3 Low	67 62 years 29% female Race NR	Gastrointestinal % Stage IV disease NR Surgery No NRS-2002	Preoperative ONS 500 ml. x 7 days (plus NJ feedings day 1-5 post-surgery) Outpatient Dietitian Oral	Preoperative dietary advice (plus NJ feedings day 1-5 post-surgery)	Adverse events Readmissions or emergency room visits Symptoms
Huang, 2020[164] (33032180) Asia Key Question 2, 3 Not conducted	114 50 years 27% female Asian	Head & Neck 0% Stage IV disease Multiple therapies No NRS-2002	Nutrition (prophylactic oral nutritional supplements) Other Dietitian/nutritionist Oral	Regular diet	Weight or body composition changes Changes in nutritional status Adverse events Survival Treatment tolerance Quality of life Symptoms

Study (PMID) **Region** **Key Question** **RoB Rating***	**Sample Size** **Age (Mean)†** **Sex (% Female)** **Race/Ethnicity**	**Cancer Type** **Stage IV Disease (%)** **Cancer Treatment Type** **Limited to Malnourished (Yes or No)** **Screening Tool**	**Intervention Type** **Intervention Delivery Setting** **Provider Delivering Intervention** **Route of Intervention**	**Comparison Description**	**Outcomes**
Jiang, 2018[167] (30633580) Asia Key Question 2, 3 Not conducted	100 Age NR 31% female Race NR	Head & Neck 57% Stage IV disease Multiple therapies No Other tool	Nutrition (oral nutritional supplement) Outpatient Multiple providers Oral	No oral nutritional supplement	Weight or body composition changes Changes in nutritional status Adverse events Quality of life
Jin, 2018[168] (30205371) Asia Key Question 2, 3 High	80 Age NR 26% female Race NR	Gastrointestinal % Stage IV Disease NR Surgery alone No Other metric	Nutrition (PN day 1 POD to 4-8 POD) Inpatient Provider NR Parenteral	Isotonic electrolyte solution	Changes in nutritional Status Quality of life
Kanat, 2013[169] (23748819) Europe Key Question 2, 3 Not conducted	69 60 years 14% female Race NR	Multiple cancers 70% Stage IV disease Multiple therapies No Screening tool NR	Nutrition ((1) megesterol acetate (MA) plus meloxicam; (2) MA plus meloxicam plus oral eicosapentaenoic acid (EPA)-enriched nutritional supplement or (3) meloxicam plus oral EPA-enriched nutritional supplement Outpatient Provider NR Oral	*No control (three treatment groups)	Weight or body Composition changes Adverse events Quality of life
Kong, 2018[52] (30055788) Asia Key Question 1 & 2, 3 High	144 Age NR 37% female Race NR	Gastrointestinal 7% Stage IV disease Surgery alone Yes Other tool	Nutrition (standard oral nutritional supplement (Ensure powder) for 2 weeks before gastrectomy and for 4 weeks postoperatively in malnourished patients) Multiple settings Dietitian/nutritionist Oral	Standard meals designed for post-gastrectomy patients	Weight or body composition changes Adverse events Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Kruger, 2016[12] (27861546) Europe Key Question 1, 3 High	100 64 years 57% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No NRS-2002	Nutrition (in-hospital peripheral intravenous nutrition on fasting days (1000 ml peripheral intravenous nutrition, 700 kcal)) Inpatient Multiple providers Parenteral	1000 ml isotonic electrolyte solution	Weight or body composition changes Quality of life
Lyu, 2022[178] (35280748) Asia Key Question 2, 3 High	222 Age NR 21% female Race NR	Gastrointestinal 0% Stage IV Multiple therapies No Multiple tools	Nutrition (enteral nutrition with ONS (Nutrison (Nutricia)) Outpatient Nutrition support team (clinicians, nutritionists, pharmacologists and nutrition nurses) Oral	Unsystematic nutrition based on general eating conditions, blood tests & treatment toxicities	Weight or body composition changes Adverse events Survival Treatment Tolerance
Meng, 2021[180] (32563598) Tan, 2021[181] (32563599) Asia Key Question 2, 3 Low	353 60 years 32% female Race NR	Gastrointestinal 7% Stage IV disease Surgery alone Yes NRS-2002	Nutrition (Oral nutritional supplements with dietary advice) Other Provider NR Oral	Dietary advice alone	Weight or body composition changes Treatment tolerance Symptoms
Okabayashi, 2011[185] (20852905) Asia Key Question 2,3 High	96 67 years 70% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No Screening tool NR	Nutrition (carbohydrate- and BCAA-enriched softpowder nutrient mixture) Inpatient Multiple providers Oral	Conventional diet with no supplementation	Weight or body composition changes Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Poon, 2004[55] (15043519) Asia Key Question 1 & 2, 3 Not conducted	88 59 years 7% female Race NR	Other 0% Stage IV disease Chemotherapy alone No Screening tool NR	Nutrition (nutritional supplementation with BCAAs twice a day in the morning and evening in addition to the usual diet) Inpatient Provider NR Oral	Standard diet	Weight or body composition changes Adverse events Survival Functional status
Ravasco, 2005[186] (15920748) Ravasco, 2005[187] (15684319) Europe Key Question 2, 3 Not conducted	75 Age NR % female NR Race NR	Head & Neck % Stage IV disease NR Radiation alone No Other tool	Nutrition ((1) diet plus regular food; (2) regular diet plus oral nutritional supplement) Outpatient Dietitian/nutritionist Oral	Regular food	Weight or body composition changes Changes in nutritional status Treatment tolerance Quality of life Symptoms
Rizvanovic, 2019[15] (31309323) Europe Key Question 1, 3 Low	50 61 years 46% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone No NRS-2002	Nutrition (400 mL of carb drink 22 h before surgery and 200 mL 2 h before anaesthesia) Inpatient Provider NR Oral	Fasted for 8 hours before surgery	Length of Stay Symptoms Functional Status
Sanchez-Lara, 2014[188] (24746976) Other Key Question 2, 3 Not conducted	92 60 years 53% female Race NR	Other 62% Stage IV Disease Chemotherapy alone No Other tool	Nutrition (oral nutritional supplement EPA) Setting NR Provider NR Oral	Standardized diets of 1400, 1600, 1800, 2000, or 2200kcal.	Weight or body composition changes Adverse events Survival Quality of life Symptoms Functional status
Sim, 2022[191] (35225460) Asia Key Question 2,3 High	58 64 years 20% female Race NR	Gastrointestinal 63% Stage IV disease Chemotherapy No Other tool	ONS twice a day (400ml, 400kcal) along with nutrition counseling and education Outpatient Multiple providers Oral	Nutrition counseling and education along with a weekly call from a trained dietitian	Changes in nutritional status Quality of Life Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Sittirai, 2021[59] (34371175) Asia Key Question 1 & 2, 3 Not conducted	126 57 years 34% female Race NR	Head & Neck 87% Stage IV disease Surgery No Screening tool NR	ONS (Immune-enhancing diet containing arginine, glutamine, and fish oil-derived fatty acids) Inpatient Provider NR Oral	Hospital-prepared blenderized diet	Adverse events Length of stay Symptoms
Tesar, 2022[17] (35258042) Europe Key Question 1, 3 Medium	120 65 years 34% female Race NR	Gastrointestinal 0% Stage IV disease Surgery No NRS-2002	ONS (oral nutritional supplements 2x a day for 7 days before surgery) Inpatient Provider NR Oral	No oral nutritional supplement	Weight or body composition changes Adverse events Length of Stay Functional status
Vidal, 2016[35] (27770454) Europe Key Question 2, 3 Not conducted	157 66 years 34% female Race NR	Other 8% Stage IV disease Surgery alone No Screening tool NR	Nutrition (TPN (Nutriflex special 70/240) for 5 days starting within 24 h after surgery) Outpatient Provider NR Parenteral	Oral nutrition alone started on day of surgery	Weight or body composition changes Survival Quality of life Functional status
Wang J, 2022[193] (35126900) Asia Key Question 2, 3 High	80 43 years 43% female Race NR	Gastrointestinal 0% Stage IV disease Multiple therapies No Screening Tool NR	Enteral nutrition (Early enteral nutrition via nasointestinal tube 12-24 hours after surgery continuously for 7 days post-surgery) Inpatient Provider NR Enteral	No enteral nutrition	Adverse events Length of stay Functional status
Wu, 2017[194] (27208039) Asia Key Question 2, 3 Medium	73 56 years 32% female Race NR	Gastrointestinal 0% Stage IV disease Surgery alone No Screening tool NR	Nutrition (EN + PN for ≥7 days; EN started within 24 hr postsurgery) Inpatient Provider NR Parenteral	EN alone for ≥7 days started within 24 hr postsurgery	Weight or body composition changes Adverse events Length of stay Quality of life

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Xie, 2021[195] (34988183) Asia Key Question 2, 3 Medium	77 62 years 19% female Race NR	Gastrointestinal 0% Stage IV disease Surgery No Screening tool NR	Intervention type (300 mL oral nutritional supplement in addition to standard diet) Other Provider NR Oral	Regular diet alone	Weight or body composition changes Adverse events Readmissions or emergency room visits Survival Length of Stay Quality of life
Yang, 2020[196] (32833549) Asia Key Question 2, 3 High	120 64 years 23% female Race NR	Gastrointestinal 61% Stage IV diseaseRadiation alone No NRS-2002	Nutrition (nutritional counseling and dietary advice + oral nutritional supplement) Outpatient Multiple providers Oral	Nutritional counseling and dietary advice	Weight or body composition changes Changes in nutritional Status Adverse events Symptoms
Zhu, 2019[200] (31464391) Asia Key Question 2, 3 Low	140 60 years 32% female Race NR	Gastrointestinal % Stage IV disease NR Surgery alone Yes NRS-2002	Nutrition (500 kcal/d total of ONS (over 3 feedings) from discharge to 90 days + nutrition education) Outpatient Physician Oral	Nutrition education	Weight or body composition changes Adverse events Quality of life Functional status
Zietarska, 2017[201] (29019951) Europe Key Question 2, 3 High	95 64 years 48% female Race NR	Gastrointestinal 32% Stage IV disease Chemotherapy alone Yes Multiple tools	Nutrition (high-energy, high-protein ONS, 250 ml/day x 3 mo.) Other Multiple providers Oral	Without nutritional support (ie, ONS)	Weight or body composition changes Changes in nutritional status Adverse events Treatment tolerance Quality of life Symptoms Functional status

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; NRS = nutritional risk screening; BCAA = branched-chain amino acid, ONS = oral nutrition supplement.

*For select studies only.

†Reports median age when mean is not available.

Multi-Component Interventions

Table F.6. Characteristics of included studies: use of multi-component interventions for cancer and treatment related symptoms (KQ3)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Baldwin, 2011[62] (21733143) Europe Key Question 1 & 2, 3 Not conducted	358 66 years 37% female Race NR	Multiple cancers % Stage IV disease NR Chemotherapy alone Yes Screening tool NR	Multi-modality ((1) dietary advice alone; (2) nutritional supplement alone; and (3) dietary and nutritional supplement) Outpatient Dietitian/nutritionist Oral	No intervention	Survival Quality of life
Demark-Wahnefried, 2008[203] (18501061) North America Key Question 2, 3 Not conducted	90 42 years 100% female Non-Hispanic White	Other 0% Stage IV disease Chemotherapy alone No Screening tool NR	Multi-modality (calcium rich diet with exercise) Outpatient Dietitian/nutritionist Oral	Calcium rich with exercise and high fruit and vegetable, low-fat diet	Weight or body composition changes Quality of life
Pettersson, 2014[216] (25467005) Europe Key Question 3 Not conducted	130 66 years 0% female Race NR	Other % Stage IV disease NR Radiation alone No Other tool	Multi-modality (advised to avoid foods high in insoluble dietary fiber and lactose during 26-month period) Outpatient Dietitian/nutritionist Oral	Usual diet, but were able to receive counseling	Symptoms
Poulsen, 2014[205] (24269077) Europe Key Question 2, 3 Not conducted	61 66 years 57% female Race NR	Multiple cancers % Stage IV disease NR Multiple therapies No NRS-2002	Multi-modality (nutritional counseling plus high-protein nutrition supplement) Outpatient Dietitian/nutritionist Oral	The control group was nutritionally instructed by the nurses with the possibility to call for a dietitian if needed	Weight or body composition changes Quality of life Symptoms

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Silander, 2012[207] (21374756) Silander, 2013[208] (23169469) Europe Key Question 2, 3 Not conducted	134 62 years 32% female Race NR	Head & Neck 74% Stage IV disease Chemotherapy alone Yes Screening tool NR	Multi-modality (nutritional counseling plus percutaneous endoscopic gastrostomy feeding Outpatient Dietitian/nutritionist Enteral	Nutritional support according to clinical praxis, which could include nutritional advice and enteral tube feeding	Weight or body composition changes Changes in nutritional status Adverse events Survival Length of stay Quality of life Symptoms Functional status
Song, 2017[210] (28943912) Asia Key Question 2, 3 Not conducted	86 56 years 48% female Race NR	Head & Neck % Stage IV disease NR Surgery alone No Other tool	Multi-modality (preoperative nutritional support therapy, postoperative nutritional therapy during hospitalization, and nutrition therapy outside the hospital) Multiple settings Multiple providers Other	Routine nutritional support therapy after surgery	Changes in nutritional status Adverse events Readmissions or emergency room visits Survival Length of stay Quality of life
Uster, 2013[211] (24103511) Europe Key Question 2, 3 Not conducted	58 65 years 21% female Race NR	Multiple cancers % Stage IV disease NR Cancer treatment type NR Yes NRS-2002	Multi-modality (standardized individual nutritional therapy, including counseling by a dietitian, food fortification, and ONS if required) Outpatient Dietitian/nutritionist Oral	Standard care	Weight or body composition changes Changes in nutritional status Quality of life Functional status

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported.
*****For select studies only.
†Reports median age when mean is not available.

Risk of Bias and Outcomes

Table F.7.1. Risk of bias assessment: use of dietary supplements for cancer and treatment related symptoms (KQ3)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Golkhalkhali, 2018[90] (928857425)	2 mo, 6 mo	Medium	Medium	Medium	Medium	Low	Low (0)	Medium
Serrano, 2022[30] (35606184)	4 wks, 12 weeks post-surgery	Low	Low	Medium	High	Low	Low (9%)	Medium
Tsuchiya, 2016[34] (27306219)	28 days	Low	Medium	High	X	X	X	High
Wang, 2017[105] (28927119)	6 months	Medium	Medium	High	Medium	Low	Low (0)	High
Wang, 2010[107] (21208095)	Inpatient	Low	Low	Low	High	Low	Low 4%	Medium

Note: X indicates domain not assessed due to previously determined high risk of bias.
Abbreviations: PMID = PubMed Identification Number; NR = not reported; KQ = Key Question.

Table F.7.2. Outcomes assessment: use of dietary supplements for cancer and treatment related symptoms (KQ3) (low and medium ROB studies)

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms	Functional Status
Golkhalkhali, 2018[90] (28857425) Medium 2 mo, 6 mo	140	Probiotic (4 wks) + 2 g. omega 3 Fas (8 wks)	Placebo	-	-	-	-	-	-	NA	↑ 2 mo ↑ 6 mo	↑	NA
Serrano, 2022[30] (35606184) Medium 4 wks, 12 weeks post-surgery	71	Protein supplementation rich in arginine and omega-6 and carbohydrate loading	One placebo to each supplement	-	-	-	-	-	-	NA	↔ FACT-G	NA	NA

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treatment Tolerance	QOL	Symptoms	Functional Status
Wang, 2010[107] (21208095) Medium Inpatient	229	Triglyceride & protein-enriched EN	Standard EN	-	-	-	-	-	-	NA	NA	↔	NA

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; BMI: body mass index; FFM: fat free mass; AE: adverse events; LOS: length of stay; QOL: quality of life; PRO: patient reported outcome; FA: fatty acid: wks: weeks: mo: month: EN: enteral nutrition; EPA: eicosapentaenoic acid; CHO: carbohydrate; ONS= oral nutrition supplement; KQ = Key Question

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer AEs, shorter LOS than comparison group).

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more AEs, longer LOS).

↔: No statistically significant difference between groups.

Table F.8.1. Risk of bias assessment: use of nutrition support including oral nutrition supplements for cancer and treatment related symptoms (KQ3)

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Chen T, 2021[159] (34237976)	1 month post-hospital discharge after surgery	Low	High	X	X	X	X	High
Chen X, 2021[8] (33752148)	Inpatient, 30 d	Low	Medium	Medium	Medium (NR)	Low	Low (2%)	Medium
Feng, 2022[48] (34362624)	Inpatient, 30 d	Low	Low	Medium	Medium	Low	Low (0)	Low
Gavazzi 2016[163] (27391922)	6 months	Low	High	X	X	X	X	High
He F, 2022[10] (35406085)	Inpatient, 30 d	Low	Low	Medium	Medium (NR)	Low	Low (2%)	Low
Jin, 2018[168] (30205371)	Inpatient	Medium	Medium	High	X	X	X	High
Kruger, 2016[12] (27861546)	X	Medium	High	X	X	X	X	High
Kong, 2018[52] (30055788)	30 days	Low	Medium	High	X	X	X	High
Lyu, 2022[178] (35280748)	After treatment completion (2-3 cycles) & up to 4 yrs	Low	Medium	High	Medium	Low	Medium (19%)	High
Meng, 2021[180] (32563598) Tan, 2021[181] (32563599)	3 mo	Low	Low	Medium	Medium	Low	Low 5%	Low

Author, Year, PMID	Outcome Timing	Selection Bias	Detection Bias	Performance Bias	Fidelity Bias	Reporting Bias	Attrition %	Overall Rating
Okabayashi, 2011[185] (20852905)	1 year	Medium	Medium	High	X	X	X	High
Rizvanovic, 2019[15] (31309323)	POD 2	Low	Low	Medium	Medium	Low	Low (0)	Low
Sim, 2022[191] (35225460)	Weeks 0, 4, 8	Medium	Medium	High	Medium	Low	High (31%)	High
Tesar, 2022[17] (35258042)	Inpatient, 30d	Medium	Medium	Medium	Medium	Low	Low (2%)	Medium
Wang J, 2022[193] (35126900)	Inpatient	Low	High	X	X	X	X	High
Wu, 2017[194] (27208039)	Inpatient; 90 d QOL	Low	Medium	Medium	Medium	Low	Medium 13%	Medium
Xie, 2021[195] (334988183)	Inpatient, 1 mo., 3 mo., 6 mo.	Low	Medium	Medium	Low	Low	Medium (14%)	Medium
Yang, 2020[196] (32833549)	3 days	Low	Medium	High	X	X	X	High
Zhu, 2019[200] (31464391)	30, 60, 90 days	LowMedium	Low	Medium	MediumLow	Low	Medium 19%	Low
Zietarska, 2017[201] (29019951)	12 weeks	Low	Low	Medium	Low	Medium	High (24%)	High

Note: X indicates domain not assessed due to previously determined high risk of bias.
Abbreviations: PMID = PubMed Identification Number; POD=postoperative day; QOL = quality of life; mo = months; d = days; KQ = Key Question.

Table F.8.2. Outcomes assessment: use of nutrition support including oral nutrition supplements for cancer and treatment related symptoms (KQ3) (low and medium ROB studies)

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QoL	Symptoms	Functional Status
Chen X, 2021[8] (33752148) Medium Inpatient, 30 d	139	Double-dose oral CHO drink before gastrectomy	Single-dose oral CHO drink before gastrectomy	-	-	-	-	-	-	NA	NA	↔	NA

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QoL	Symptoms	Functional Status
Feng, 2022[48] (34362624) Low Inpatient, 30 d	126	Preoperative oral CHO 200 ml 2-3 hr. before surgery & postoperative early oral feeding	Fasted pre-surgery (> 8 hrs.) + TPN x 24 hr. post-surgery	-	-	-	-	-	-	NA	NA	↑ nausea	NA
He F, 2022[10] (35406085) Low Inpatient, 30 d	67	Preoperative ONS 500 ml. x 7 days	Dietary advice	-	-	-	-	-	-	NA	NA	↔	NA
Meng, 2021[180] (32563598) Tan 2021[181] (32563599) Low	353	Oral nutritional supplements with dietary advice	Dietary advice alone	-	-	-	-	-	-	↑ Chemotherapy modifications, delays, dose reductions, terminations	NA	↑ fatigue, appetite loss	NA
Rizvanovic, 2019[15] (31309323) Low POD 2	50	Preop. oral CHO supplement	Preop. fasting	-	-	-	-	-	-	NA	NA	↑ nausea ↔ vomiting ↔ pain	↑

Author, Year, RoB Timing	N	Treatment	Control	Weight/ Body Comp.	Changes in Nutr. Status	Adverse Events	Readmissions/ Emergency Room Visits	Survival	LOS	Treat. Tolerance	QoL	Symptoms	Functional Status
Tesar, 2022[17] (35258042) Medium Inpatient, 30d	120	oral nutritional supplements 2x a day for 7 days before surgery	No oral nutrition supplement	-	-	-	-	-	-	NA	NA	NA	↔ Barthel Index
Wu, 2017[194] (27208039) Medium Inpatient	80	Post-op EN+PN via NJT/ j-tube	Post-op EN via NJT/ j-tube	-	-	-	-	-	-	NA	UTD	NA	NA
Xie, 2021[195] (33498183) Medium Inpatient, 1 mo., 3 mo., 6 mo.	77	300 mL oral nutritional supplement in addition to standard diet	Regular diet alone	-	-	-	-	-	-	NA	↔ **EORTC QLQ-C30**	NA	NA
Zhu, 2019[200] (31464391) Low 30-90 days	140	500 kcal ONS 3x/d x 90d + dietary advice from doctor at discharge	Dietary advice from doctor at hospital discharge	-	-	-	-	-	-	NA	EQ-5D ↔ 30d ↔ 60d ↔ 90d	NA	↔ grip

Abbreviations: PMID = PubMed Identification Number; ROB=risk of bias; POD = postoperative day; AE = adverse events; BMI: body mass index; FFM: fat free mass; FM = fat mass; LOS: length of stay; QOL: quality of life; PRO: patient reported outcome; EN: enteral nutrition: PN: parenteral nutrition: ONS: oral nutritional supplement: EQ-5D: EuroQoL-5D: UTD: unable to determine: CHO: carbohydrade: BW: body weight; d: day; NJT = nasojejunal tube; NA=not assessed.

-: Not applicable

↑: Intervention group had a statistically significantly better outcome than comparison group (e.g. fewer AEs, shorter LOS than comparison group).

↓: Intervention group had a statistically significantly worse outcome than comparison group (e.g. more AEs, longer LOS).

↔: No statistically significant difference between groups.

Appendix G. Evidence Tables for Chapter 9

Special Diets

Table G.1. Characteristics of included studies: special diets (KQ4)

Study (PMID) Region Key Question RoB Rating*	Sample Size Age (Mean)† Sex (% Female) Race/Ethnicity	Cancer Type Stage IV Disease (%) Cancer Treatment Type Limited to Malnourished (Yes or No) Screening Tool	Intervention Type Intervention Delivery Setting Provider Delivering Intervention Route of Intervention	Comparison Description	Outcomes
Cho, 2022[217] (35845810) Asia Key Question 4 Not conducted	78 60 years 100% females Race/ethnicity NR	Other 0% Stage IV Chemotherapy No Screening tool NR	Mediterranean diet + advice (1500 kcal/d) Other/Home (delivered 10 meals/week) Nutritionist Oral	Dietary advice (1500 kcal/d) Home	Weight or body composition changes
Harvie, 2022[218] (34912072) Europe Key Question 4 Not conducted	172 52 years 100% female 91% white	Other 0% Stage IV Chemotherapy No Screening Tool NR	Intermittent 25% energy restriction (Mediterranean diet 5d/wk. + low energy, low CHO diet 2d/wk.) + Physical activity program Outpatient Dietitian Oral	Continuous 25% energy restriction (Mediterranean diet) + physical activity program	Weight or body composition changes Symptoms Treatment tolerance
Vafa, 2020[215] (32898787) Asia Key Question 3, 4 Not conducted	135 53 years 100% female Race NR	Other 0% Stage IV disease Multiple therapies No Screening tool NR	Special Diets (Calorie restricted diet + CFU symbiotic supplement) Outpatient Not reported Oral	placebo	Weight of body composition changes Quality of life
Villarini, 2012[219] (22896285) Europe Key Question 4 Not conducted	94 51 years 100% female Race NR	Other 0% Stage IV disease Multiple therapies No Screening tool NR	Special diets (Mediterranean diet) Outpatient Multiple providers Oral	General recommendations for the prevention of cancer and a baseline brief kitchen course	Weight or body composition changes

Abbreviations: KQ = Key Question; PMID = PubMed Identification Number; NR = not reported; CFU = colony forming unit.
*For select studies only.
†Reports median age when mean is not available.

Appendix H. References for Appendixes C–G

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